Chemoenzymatic Syntheses of Biologically Active Natural Products

A Thesis submitted for the degree of
Doctor of Philosophy of the Australian National University

By

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2005-2008 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Kerrie Austin
January 2009

"I could recount an endless number of stories about carbon atoms that become colours or perfumes in flowers; of others which, from tiny algae to small crustaceans to fish, gradually return as carbon dioxide to the waters of the sea… Instead, I will tell just one more story…"

Primo Levi in The Periodic Table, 1975

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Publications and Presentations

The following list details the publications, patents and presentations that have resulted from research performed during the candidature of the Doctor of Philosophy.

Publications:[➢]

i) Austin, K. A. B.; Matveenko, M.; Reekie, T. A.; Banwell, M. G., Chemoenzymatic methods for enantioselective assembly of biologically active natural products, *Chemistry in Australia*, **2008**, 75, 3 – 7.

ii) Austin K. A. B.; Banwell, M. G.; Willis, A. C., A formal total synthesis of platencin, *Organic Letters*, **2008**, 10, 4465 - 4468.

iii) Reekie, T. A.; Austin, K. A. B.; Banwell, M. G.; Willis, A. C., The chemoenzymatic total synthesis of phellodonic acid, a biologically active and highly functionalized hirsutane derivative isolated from the Tasmanian fungus *Phellodon melaleucus*, *Australian Journal of Chemistry*, **2008**, 61, 94 – 106.

iv) Banwell, M. G.; Austin K. A. B.; Willis, A. C., Chemoenzymatic total syntheses of the linear triquinane-type natural products (+)-hirsutic acid and (−)-complicatic acid from toluene, *Tetrahedron*, **2007**, 63, 6388 – 6403.

v) Austin, K. A. B.; Banwell, M. G.; Harfoot, G. J.; Willis, A.C., Chemoenzymatic syntheses of the linear triquinane-type sesquiterpenes (+)-hirsutic acid and (-)-complicatic acid, *Tetrahedron Letters*, **2006**, 47, 7381 – 7384.

vi) Austin, K. A. B.; Banwell, M. G.; Willis, A. C., Synthesis and X-ray crystal structure of a cyclic hemiorthoester, *ARKIVOC*, **2006**, 13, 1 – 7.

Patents:

i) Austin K. A. B.; Banwell, M. G., Process for the synthesis of platencin and analogues thereof, Australian Provisional Patent Application No. 2008903689, Filing date 18/07/2008.

[➢] Full copies of each of these publications are provided in PDF format on the Compact Disc found on the inside back cover of this thesis.

Presentations:

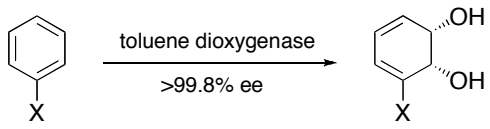
i) Austin K. A. B.; Banwell, M. G., A formal total synthesis of platencin. Poster presentation at the Gordon Research Conference on Natural Products Chemistry, New Hampshire, America, July 2008.

ii) Austin K. A. B.; Banwell, M. G., Exploiting the whole cell biotransformation of arenes as a source of enantiomerically pure building blocks for the synthesis of sesquiterpenoid natural products. Oral presentation delivered at the 22nd Royal Australian Chemical Institute Organic and Physical Chemistry Conference, Adelaide, Australia, January 2007, p.17.

iii) Austin, K. A. B.; Banwell, M. G.; Harfoot, G. J.; Willis, A.C., A Chemoenzymatic total synthesis of (-)-complicatic acid. Poster presentation at Frontiers of Mass Spectrometry, Drug Design and Synthesis, Halpern Symposium, Wollongong, Australia, November 2005, p.76.

Abstract

Various genetically modified micro-organisms that over-express dioxygenase-type enzymes can be used for the whole-cell biotransformation of a wide range of arenes (**1**) into the corresponding *cis*-1,2-dihydrocatechols (**2**). These metabolites, which are obtained in enantiopure form, can serve as valuable starting materials for the chemical synthesis of a wide-range of biologically active natural products and related species.

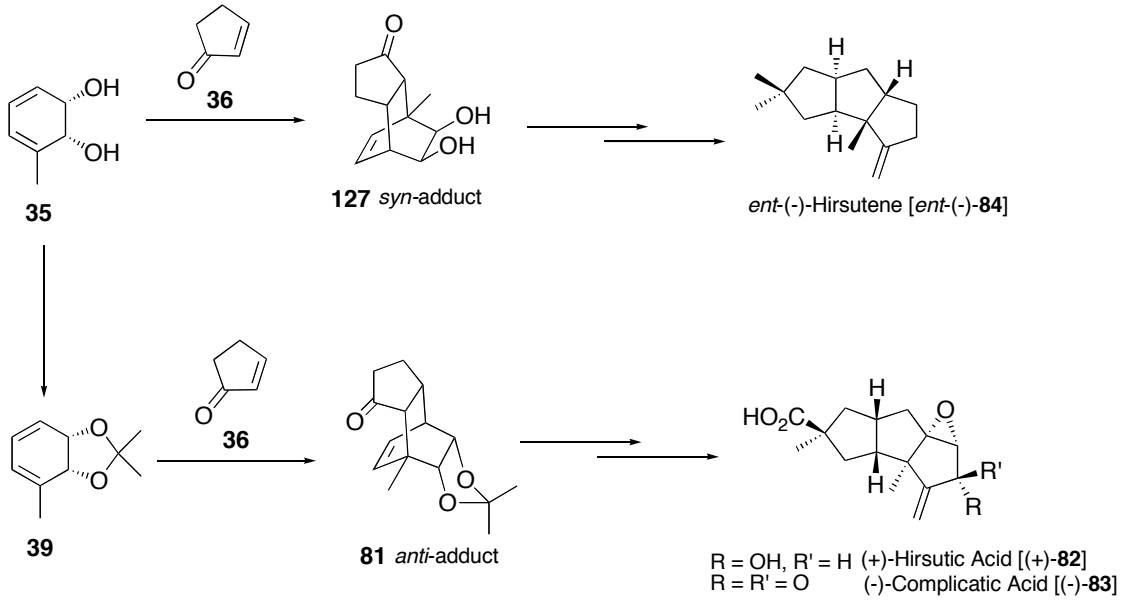


1 **2**

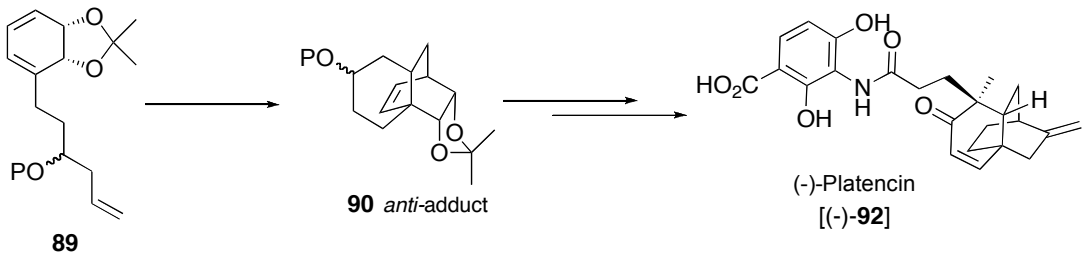
X = H, Me, Cl, Br, I, CN, $CH{=}CH_2$ *etc.*

This thesis reports on a series of studies, encompassing both natural product synthesis and methodological development, that were undertaken with the broad objective of investigating new uses and applications of *cis*-1,2-dihydrocatechols in organic synthesis. In particular, this thesis describes a thorough investigation into the value of employing these compounds in facially selective Diels-Alder cycloaddition reactions and the utilisation of the resulting adducts in the synthesis of the sesquiterpenoid natural products (+)-hirsutic acid, (-)-complicatic acid and (-)-platencin.

One limitation of the use of enzymatically derived *cis*-1,2-dihydrocatechols as starting materials in total synthesis is that, in most cases, only one enantiomer of the metabolite is produced during the biotransformation. Generally, this limitation means that only one enantiomeric form of any target natural product can be accessed. In many instances it has, therefore, only been possible to synthesise the non-natural enantiomer of certain natural products. The research presented in Chapter Two of this Thesis demonstrates that such constraints can be overcome using facially selective Diels-Alder cycloaddition reactions. Specifically, the application of *cis*-1,2-dihydrocatechol **39** in an *anti*-selective intermolecular Diels-Alder reaction is shown to allow for the total syntheses of the natural enantiomeric forms of the linear triquinane-type natural products (+)-hirsutic acid [(+)-**82**] and (-)-complicatic acid [(-)-**83**]. This work follows on from previous studies undertaken in the Banwell group, in which the non-natural enantiomeric form of the linear triquinane hirsutene [*ent*-(-)-**84**] was synthesised *via* a *syn*-selective Diels-Alder reaction involving the SAME metabolite (**35**).



Although *inter*molecular Diels-Alder reactions of *cis*-1,2-dihydrocatechols have been well studied and found extensive use in total syntheses, the corresponding *intra*molecular process has been used to a lesser extent. The work presented in Chapter Three provides a detailed characterisation of the intramolecular cycloaddition reactions of *cis*-1,2-dihydrocatechols, demonstrating that the facial selectivity of these reactions can be controlled in an analogous manner to the intermolecular variant. These protocols have been utilised, as detailed in Chapter Four, in an enantioselective total synthesis of the recently discovered antibacterial natural product (-)-platencin [(-)-**92**]. Specifically, *cis*-1,2-dihydrocatechol derivative **89** is shown to undergo a facially selective intramolecular Diels-Alder reaction to afford cycloadduct **90**, which is then elaborated to the carbocyclic core structure of this potent antibacterial agent.



Glossary

The following abbreviations have been used throughout this thesis:

δ	chemical shift (parts per million)
ºC	degrees Celcius
λ	wavelength (nm)
λ_{max}	wavelength of maximum absorption (nm)
$\lambda_{transmission}$	wavelength of transmission (nm)
μg	microgram(s)
μL	microlitre(s)
Ac	acetyl
AcOH	acetic acid
AIBN	2,2'-azobis*(iso*butyronitrile)
APT	attached proton test (^{13}C NMR spectroscopy)
aq.	aqueous
Ar	unspecified aryl group
atm	atmosphere(s)
BDMA	benzaldehyde dimethylacetal
BHT	2,6-di-*t*-butyl-methylphenol
Bn	benzyl
BOM	benzyloxymethyl
br	broad
Bu	butyl
n-Bu	*normal*-butyl
s-Bu	*secondary*-butyl
t-Bu	*tertiary*-butyl
c	concentration (g/100 mL)
ca.	*circa* (approximately)
cat.	catalytic/catalyst
CBS	Corey-Bakashi-Shibata (conditions for an asymmetric reduction)
cf.	*confer* (compare)
cm	centimetre(s)
Cod	1,5-cyclooctadiene
conc.	concentrated
COSY	^{1}H-^{1}H correlation spectroscopy
CSA	(1*S*)-(+)-10-camphor sulfonic acid

d	doublet
DA	intermolecular Diels-Alder
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
c-DHC	*cis*-1,2-dihydrocatechol
DIBAL-H	di*iso*butylaluminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DVK	divinyl ketone
ee	enantiomeric excess
e.g.	*exempli gratia* (for example)
EI	electron impact (mass spectrometry)
equiv.	equivalents
ES	electrospray (mass spectrometry)
Et	ethyl
et al.	*et alia* (and others)
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
ETSA	ethyl(trimethylsilyl)acetate
eV	electron volt(s)
FGI	functional group interconversion
g	gram
GC	gas chromatograpy
gem	geminal
gen.	generation
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry

hν	light
Hz	Hertz
IMDA	intramolecular Diels-Alder
IBX	2-iodobenzoic acid
IR	infra red
J	^{1}H-^{1}H coupling constant
kbar	kilobar(s)
KHMDS	potassium bis(trimethylsilyl)amide
L	litre(s)
LDA	lithium di*iso*propylamide
LiHMDS	lithium bis(trimethylsilyl)amide
lit.	literature value
LiTMP	lithium 2,2,6,6-tetramethylpiperidine
LRMS	low resolution mass spectrometry
m	multiplet
M	molar
M^{+}	molecular ion
Me	methyl
MeOH	methanol
MEM	(2-methoxyethoxy)methoxy
MHz	mega-Hertz
min	minute(s)
mL	millilitre(s)
mm	millimetre(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point (ºC)
MS	mass spectroscopy
m/z	mass-to-charge ratio
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
ODPM	oxa-di-π-methane
ORTEP	Oak Ridge Thermal Ellipsoid Plot
P	unspecified protecting group

p	para
PCC	pyridinium chlorochromate
Ph	phenyl
plc	preparative layer chromatography
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
i-PrMgCl	*iso*-propyl magnesium chloride
q	quartet
qu	quintet
quant.	quantitative
ref.	reference
R	unspecified alkyl group
R_f	thin layer chromatography retardation factor
r.t	room temperature
s	singlet
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
t	tertiary
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TDO	toluene dioxygenase
TEAD	bis-(2,2,2-trichloroethyl) azodicarboxylate
temp.	temperature (ºC)
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THS	*t*-hexyldimethylsilyl
TIPS	tri*iso*propylsilyl
tlc	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

TsOH	toluenesulfonic acid
UV	ultra violet (spectroscopy)
viz.	*videlicit* (that is, namely)
vs.	*versus*
v/v	unit volume per unit volume (ratio)
W	watt(s)
w/v	unit weight per unit volume (%)

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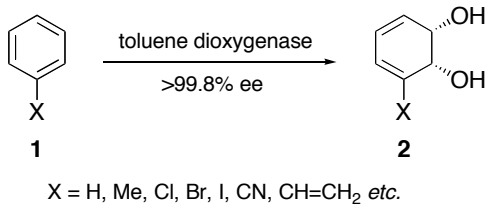
CHAPTER ONE

Introduction: cis-*1,2-Dihydrocatechols and their use in Diels-Alder Cycloaddition Reactions*

1.1 Enzymatic Production of *cis*-1,2-Dihydrocatechols from Arenes

The ability of microbes to metabolise aromatic hydrocarbons was first demonstrated in 1908 when Stromer *et al*. reported the isolation of a bacterial strain, *Bacillus hexacarbovorum*, able to grow using toluene or xylene as a carbon source.[1] The risk that aromatic hydrocarbons pose in the environment has resulted in much investigation into the microbial degradation of these compounds and the various metabolic pathways involved in such processes.[2] Gibson *et al*. elucidated one of these pathways in 1968, showing that degradation of several aromatics by the soil bacterium *Pseudomonas putida* proceeds *via* dihydroxylation of the aromatic ring and subsequent dehydrogenation of this primary metabolite to the corresponding catechol.[3,4] The enzyme responsible for the initial dihydroxylation process was identified as toluene dioxygenase (TDO).[4,5] In later studies, a chemically mutated strain (39D) of *P. putida* was identified that lacked the dehydrogenase responsible for the conversion of the primary oxidation product into the catechol. This mutation resulted in the accumulation of the initial oxidation product, which was then characterised as *cis*-1,2-dihydrocatechol **2** (Scheme 1.1).[6] Throughout this Thesis the term *c*-DHC will used as an abbreviation *cis*-1,2-dihydrocatechols of this type.



Scheme 1.1: *Production of various* c-*DHC derivatives from the corresponding arenes by toluene dioxygenase.*

Since these initial observations, a number of other dioxygenase-type enzymes have been identified that utilise polynuclear arenes as substrates. Naphthalene dioxygenase is an example of such a species.[5] Metabolites produced by the action of dioxygenases on various aromatics are highly sought after in organic synthetic chemistry for a number or reasons.[7-10] Firstly, the dihydroxylation occurs in a completely regio- and enantio-selective manner affording single and enantiopure products.[11] Secondly, this process is one of only a few known that is able to disrupt the highly stable aromatic system. Finally, the array of functional groups generated in the products is useful for further transformations. In order to exploit this potential, the genes encoding for various dioxygenases have been cloned and recombinantly expressed in host organisms such as laboratory strains of *Escherichia coli*, including the widely used JM109 (pDTG601) strain.[12] These recombinant micro-organisms over-express the cloned dioxygenases, but lack the dehydrogenase necessary for the subsequent dehydrogenation of the primary dihydocatechol, thereby allowing for highly efficient production of significant amounts (up to 35 g per litre of fermentation broth) of enantiopure *c*-DHCs (>99% ee). The range of aromatics that can be converted into *c*-DHCs by this process is remarkably broad, with more than 300 metabolites having been reported to date.[5,10,11] A small selection of these metabolites is shown in Figure 1.1.

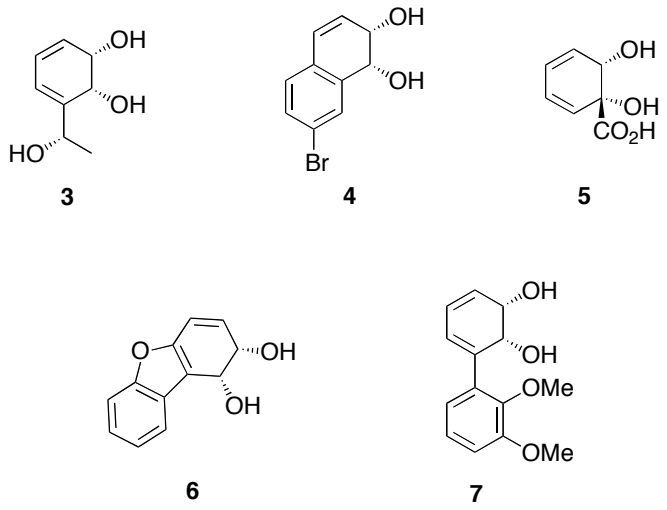


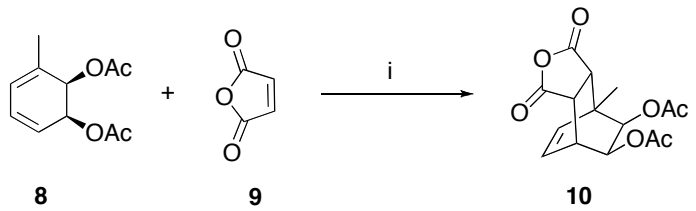
Figure 1.1*: Examples of c-DHCs that demonstrate the structural diversity of the substrates processed by toluene, naphthalene and related dioxygenases.*

Nevertheless, there are some limitations to the enzymatic transformations of arenes into *c*-DHCs. Firstly, the efficiency and enantioselectivity of these transformations is dependant on the substituents on the aromatic ring.[11] While a large variety of *c*-DHCs have been obtained in high enantiomeric excesses, there are also examples where this biotransformation proceeds in a less enantioselective manner or, sometimes, not at all. Secondly, in most cases this process only

allows access to one enantiomeric form of the *c*-DHC. Although some *c*-DHC derivatives have been chemically manipulated to produce the opposite enantiomer, in a method called "enantiomeric switching",[13] the yields are often poor and the additional chemical steps detract from the convenience of the one-step microbial generation of the *c*-DHC. Despite these limitations, the metabolites described here have been used successfully as starting materials in the development of concise, enantiospecific syntheses of various structurally demanding and biologically active natural products.[10]

1.2 *cis*-1,2-Dihydrocatechols as 4π-Addends in Diels-Alder Cycloaddition Reactions

The endocyclic 1,3-diene moiety of *c*-DHC derivatives readily participates in Diels-Alder cycloaddition reactions with a wide range of electron-deficient dienophiles.[∞] This capacity has been recognised since the discovery of *c*-DHCs by Gibson and co-workers, when the corresponding Diels-Alder adducts were used to assist in assigning the stereochemistry of the first examples of these metabolites (Scheme 1.2).[6,14] The bi- or tri-cyclic products obtained from this reaction are enantiomerically pure and highly functionalised systems, making them valuable compounds for use in enantioselective total synthesis. As a result, there has been much research into exploiting the cycloaddition reactions of *c*-DHCs. Both inter- and intra-molecular Diels-Alder reactions of *c*-DHCs have been reported,[7] although the intramolecular variants have been studied in much less detail. This Section outlines the work that has been carried out in this area to date. However, it is first appropriate to review the stereoselectivities associated with the Diels-Alder reaction in general.



8 **9** **10**

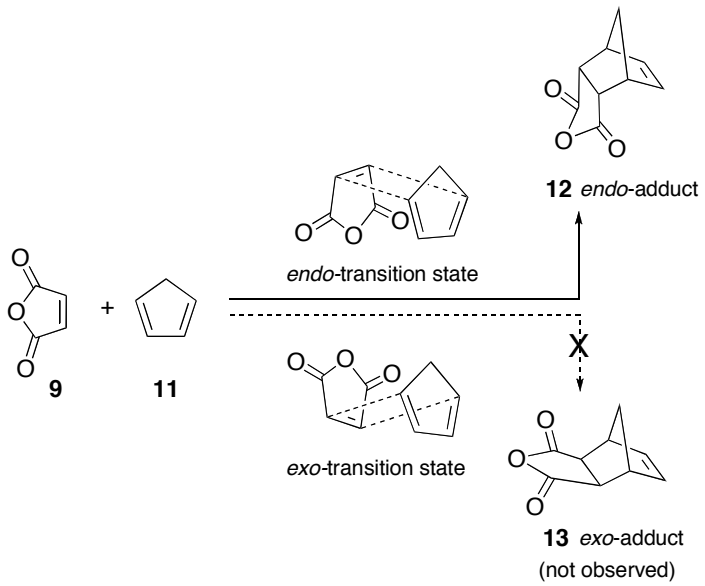
Scheme 1.2: *Reagents and conditions* (i) benzene, r.t., 6 days.

∞ The less substituted olefinic bond of *c*-DHCs has also been observed to function as a dienophile in Diels-Alder reactions with various dienes.[10] These examples will not be covered in this Section, which focuses only on their use as the diene component of cycloaddition reactions.

1.2.1 Selectivity in Diels-Alder cycloaddition reactions

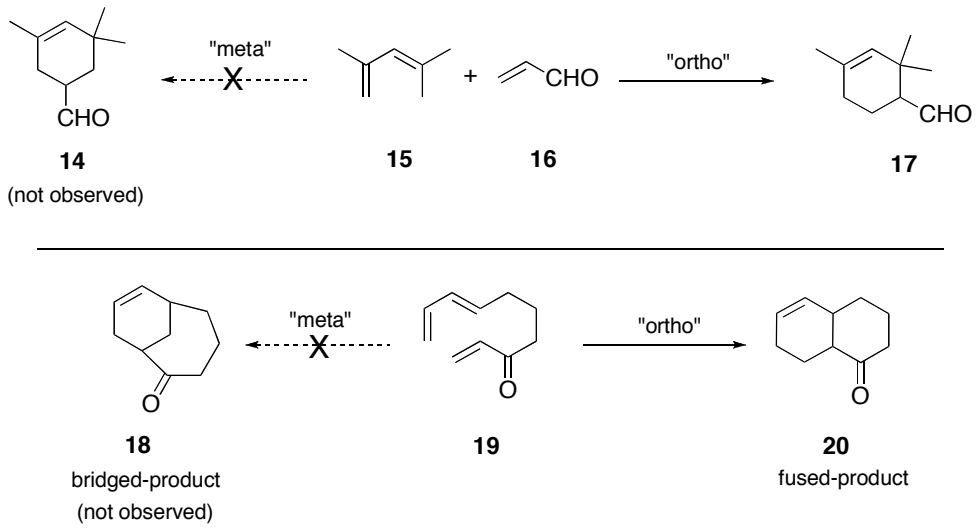
There are three principal selectivity issues associated with the Diels-Alder cycloaddition reaction: diastereoselectivity (*endo*/*exo*), regioselectivity (*ortho*/*meta*) and facial selectivity (*syn*/*anti*). All three aspects must be taken into account when considering the possible products of any given Diels-Alder cycloaddition reaction involving *c*-DHCs.

The diastereochemical (*endo*/*exo*) outcome of any Diels-Alder cycloaddition reaction reflects the orientation of the dienophile with respect to the diene at the transition state.[15] *endo*-Addition involves orientation of the dienophile such that the substituent bearing the π-bond is positioned *towards* the diene. In contrast, *exo*-addition involves orientation of the dienophile such that the substituent bearing the π-bond is positioned *away* from the diene. In the intermolecular Diels-Alder reaction the *endo*-orientation is normally preferred. As a result, the *endo*-adduct is observed in the majority of cases. Accordingly, the Diels-Alder reaction between cyclopentadiene and maleic anhydride affords cycloadduct **12** as the exclusive product of the reaction (Scheme 1.3).[16] This preference for the *endo*-transition state can be explained in terms of maximisation of the secondary orbital overlap and is known as the '*endo* rule'.[17,18] However, this rule does not reliably predict the diastereochemical outcome of intramolecular Diels-Alder cycloaddition reactions. Indeed, mixtures of *endo*- and *exo*-adducts are often obtained from these reactions.[19]



Scheme 1.3: *The Diels-Alder cycloaddition reaction between maleic anhydride (**9**) and cyclopentadiene (**11**).*

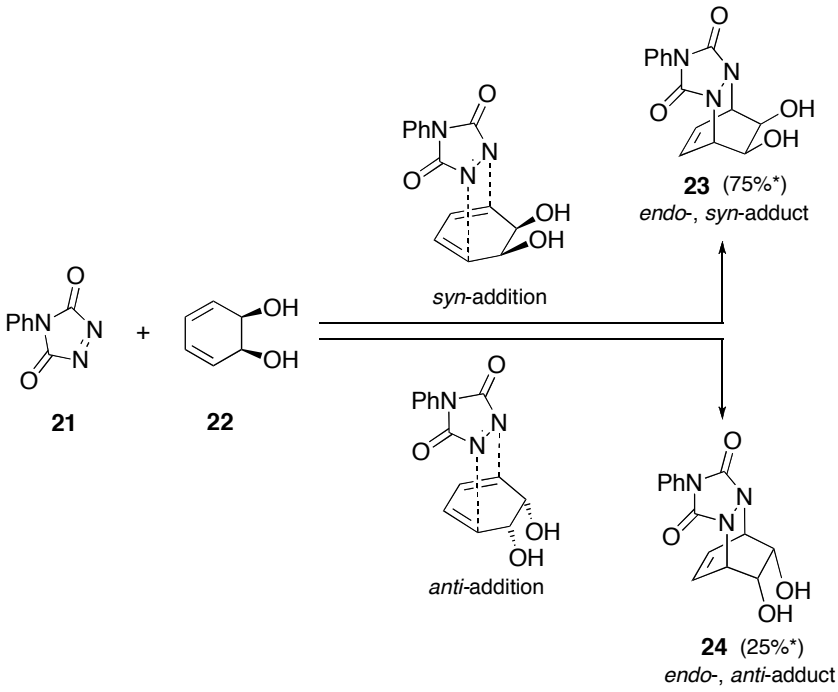
Two regiochemical (*ortho*/*meta*[✡]) outcomes are possible if asymmetrical dienes and/or dienophiles are employed in a Diels-Alder reaction. Despite the possibility of mixtures of regioisomers being produced, these cycloadditions have been found to be highly regioselective in most cases.[15] The propensity for *ortho*- or *meta*-selectivity varies with the substituents on both the diene and the dienophile. However, the *ortho*-adduct is generally preferred (see Scheme 1.4 for examples of this).[20,21] This *ortho*-preference has been attributed to the matching of complementary orbital coefficients in combination with secondary orbital interactions[22] and is known as the '*ortho* effect'. However, in the intermolecular reaction, if the diene and/or the dienophile have more than one substituent, problems of regioselectively are often encountered and mixtures of products are frequently obtained. In contrast, the regioselectively of the intramolecular reaction is largely controlled by the conformational constraints imposed by the connecting chain/tether. Specifically, if the tether is short then only one regioisomer is possible regardless of the substituents on the diene or the dienophile[23] (Scheme 1.4).[21] In contrast, the regioselectivity of this reaction is less predictable when longer tethers (>10 carbon atoms in the chain) are used.[15]



Scheme 1.4: *Examples of* ortho-*outcomes of Diels-Alder reactions for which two regioisomeric products are possible.*

✡ The terms *ortho* and *meta* refer to the relative positions of terminal substituents from the diene and the dienophile on the newly formed cyclohexene ring of the Diels-Alder adduct.

Finally, when there are stereogenic centres associated with either the diene or dienophile the facial selectivity (*syn*/*anti*) of the reaction must be considered. The components of the reaction may approach each other from either the more or less sterically hindered face in processes known as *syn*- and *anti*-addition, respectively. The facial selectivity of a given Diels-Alder reaction is determined through the interplay of steric, orbital and electrostatic factors. The outcome of a given reaction is, therefore, difficult to predict and mixtures of compounds are often obtained (see Scheme 1.5 for an example).[24] Steric interactions are considered to be the most influential of these factors. However, when these are minimal, other effects can play a decisive role in dictating the facial selectivity of the Diels-Alder reaction. Many interactions have been cited to explain the facial selectivities observed for various systems and in 2000 Mehta and Uma proposed the hierarchy of these effects to be steric > through space interactions (electrostatic repulsion/attractive stabilising orbital interactions) > hyperconjugative effects > ground-state orbital distortions (generally in substrates devoid of polar substituents).[25]



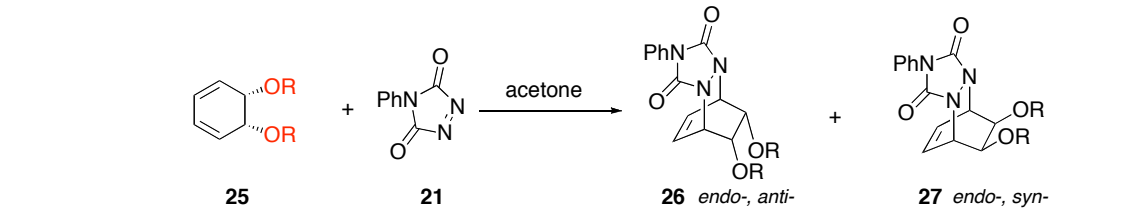
Scheme 1.5: *The Diels-Alder reaction between 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**21**) and c-DHC **22** (*relative proportions of cycloadducts, not yields).*

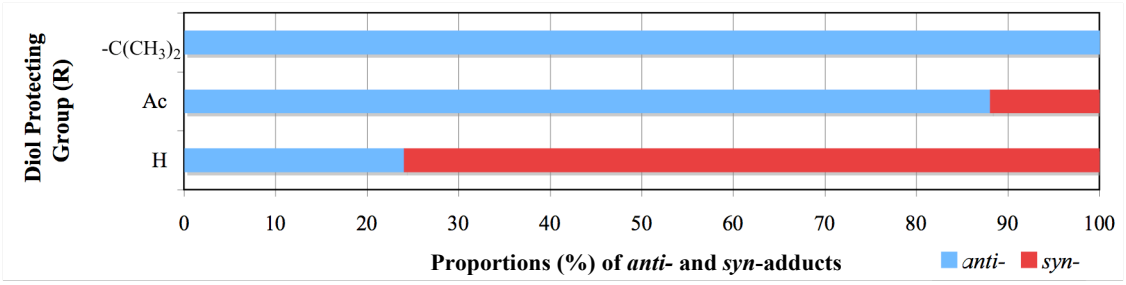
1.2.2 Intermolecular Diels-Alder (DA) reactions of *cis*-1,2-dihydrocatechols

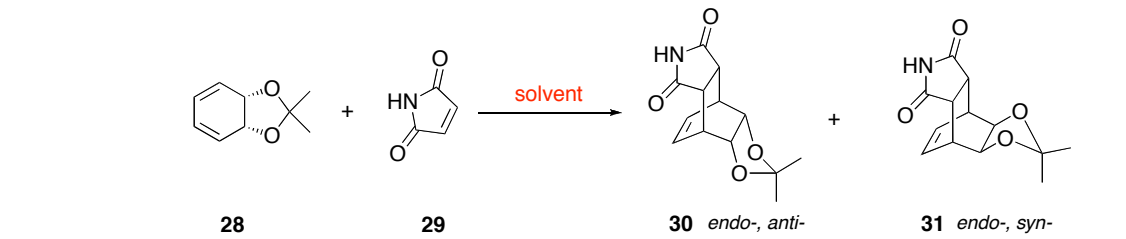
The intermolecular Diels-Alder (DA) cycloaddition reactions of *c*-DHCs have been studied extensively. Both acylic and cyclic dienophiles incorporating various combinations of carbon, nitrogen and oxygen have been investigated, along with alkynes and nitriles. Furthermore, the DA reactions of both free diol and protected derivatives of the *c*-DHCs have been examined. Due to the large number of examples, this Section does not provide a comprehensive account of all the reported DA reactions of *c*-DHCs. For this the reader is directed towards the reviews published in the area.[7-10] This Section simply provides an introduction to the various stereochemical outcomes obtained when *c*-DHCs participate in DA cycloaddition reactions.

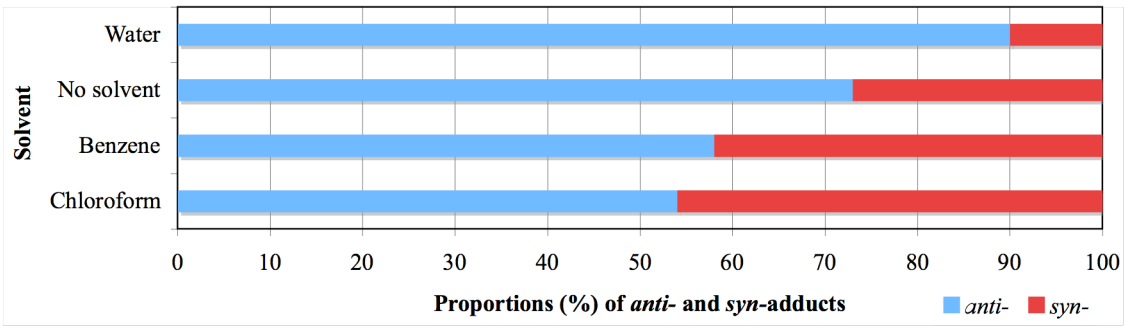
The selectivities associated with the DA reactions of *c*-DHCs are well established. These processes proceed with excellent regio- and diastereo-selectivity to afford, in the majority of cases, the *ortho*-, *endo*-adducts. The factors that govern these stereochemical outcomes have been discussed in the previous Section and the observed selectivities are consistent with the ascribed explanations. Conversely, the facial selectivity observed for these reactions is less obvious and has therefore been the subject of a number of studies by various groups. Many of these investigations demonstrated that the diol protecting group has a major influence on the facial selectivity of the reaction. While free *c*-DHCs tend to undergo cycloaddition to the face *syn* to the diol, protected derivatives often demonstrate a preference for *anti*-addition. Further to this, the dienophile and the solvent have also been observed to influence the facial selectivity of the reaction. Burnell *et al*. have recently published a systematic study demonstrating how each of these three aspects can have a dramatic effect on the facial selectivity observed for these cycloaddition reactions.[24] Some of their results are presented in Figure 1.2.

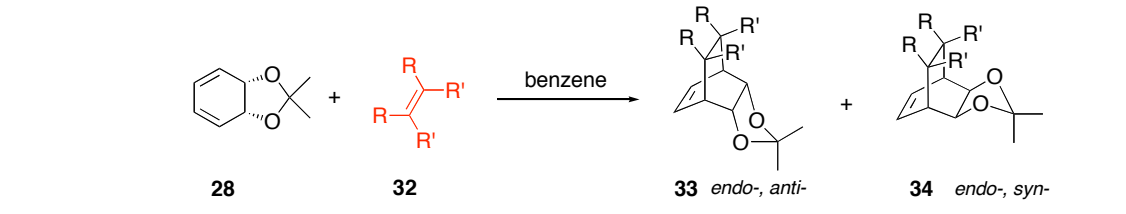
Figure 1.2: *The effect of the diol protecting group, solvent and dienophile on the* anti-/syn- *ratio of selected intermolecular Diels-Alder reactions of c-DHCs.*

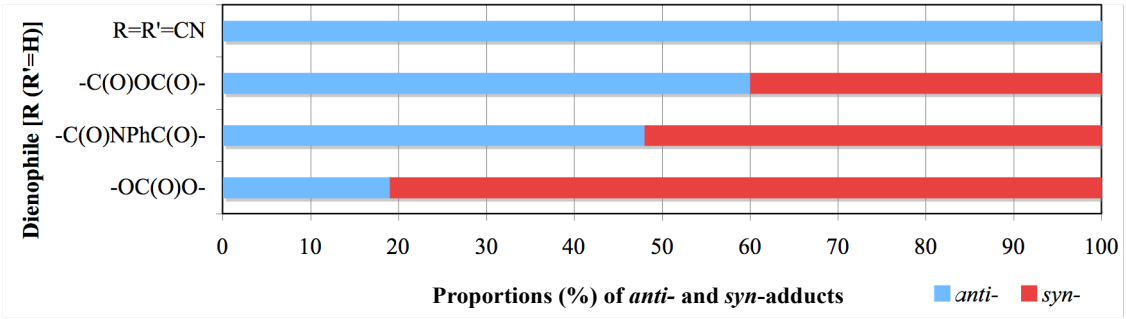




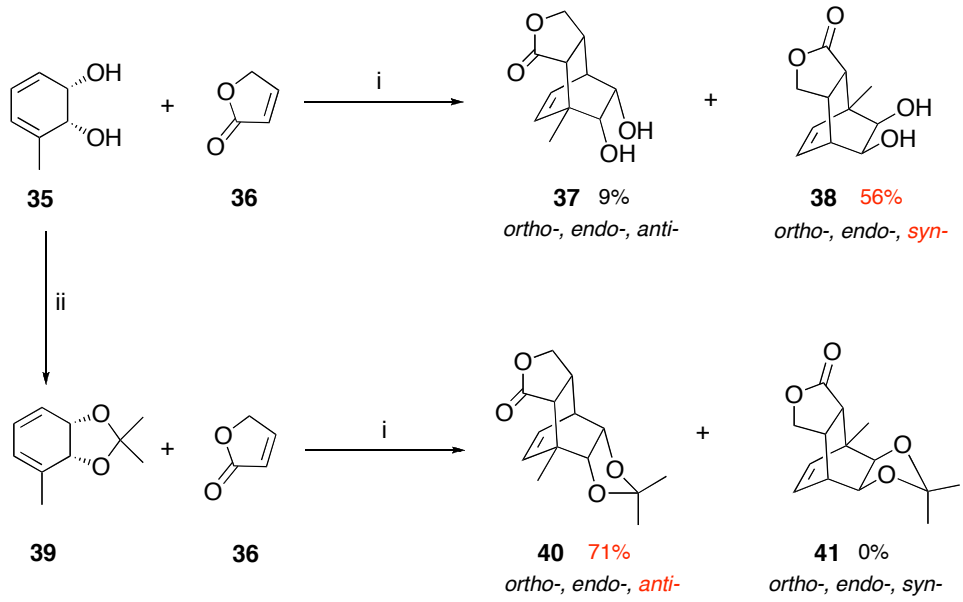








The selection of examples in Figure 1.2 were chosen to demonstrate that through the correct choice of reaction conditions products from either *syn*- or *anti*-addition pathways can be prepared quite selectively. Of course, control of the facial selectivity in this manner is extremely desirable. However, due to the instability of *c*-DHCs these reactions are usually carried out at room temperature, limiting the basic reaction to examples involving highly reactive dienophiles.[∝] Stewart has demonstrated that in cases where less reactive dienophiles such as cyclopenten-2-one or 2(5*H*)-furanone are required, the reaction can be promoted by high-pressure techniques.[26] The facial selectivity was found to be analogous to that observed under conventional conditions. Thus, the use of unprotected *c*-DHC **35** in a high-pressure promoted Diels-Alder reaction with 2(5*H*)-furanone (**36**) was found to favour formation of the *syn*-adduct **38** while the acetonide-protected derivative **39** preferentially formed the *anti*-adduct **40** (Scheme 1.6). The reaction was also found to be regio- and stereo-selective proceeding *via* an *endo*-, *ortho*- transition state.

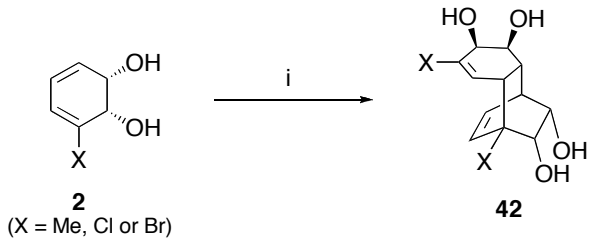


Scheme 1.6: *Reagents and conditions* (i) 19 kbar, CH_2Cl_2, 18 ºC, 16 h; (ii) $(MeO)_2CMe_2$, *p*-TsOH•H_2O, -10 to 18 ºC, 24 h.

Stewart reported that dimerisation of the *c*-DHC was also observed to form compounds of the general type **42** (Scheme 1.7).[26] This reaction was found to be highly stereoselective. In every instance, the only dimer isolated was the result of *anti*-addition of both the diene and the

∝ Lewis acids cannot be employed to catalyse such reactions, as *c*-DHCs are known to undergo rapid dehydration and accompanying aromatisation in the presence of acid.

dienophilic partners, irrespective of whether the free diol or its hydroxyl-protected derivative was used. Dimerisations of derivatives of *c*-DHC **2** have been reported by a number of groups[27-29] and provide examples of DA reactions of *c*-DHCs in which the dienophile also possesses stereogenic centres. In all cases, these cycloaddition reactions were observed to be highly *anti*-selective, with respect to both partners.



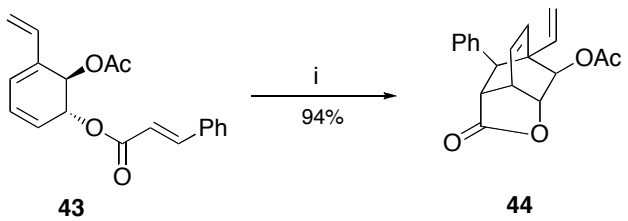
2
(X = Me, Cl or Br)

42

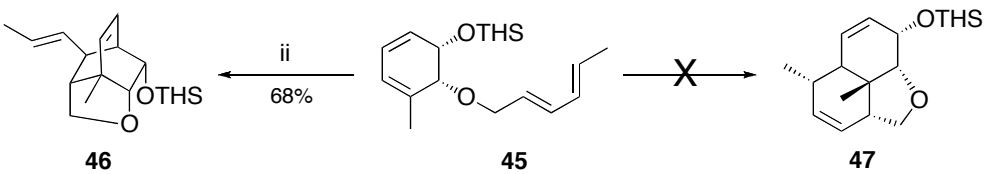
Scheme 1.7: *Reagents and conditions* (i) 19 kbar, CH_2Cl_2, 18 ºC, 16 h.

1.2.3 Intramolecular Diels-Alder (IMDA) reactions of *cis*-1,2-dihydrocatechols

In contrast to the *inter*molecular (DA) process, the *intra*molecular Diels-Alder (IMDA) cycloadditions of *c*-DHCs remain largely unexplored, with only a handful of examples reported in the literature. The first of these were published by Hudlicky and co-workers and employed dienophiles tethered at one of the hydroxy groups of the *c*-DHC framework *via* either an ester (**43**) or an ether (**45**) linkage (Scheme 1.8).[30,31]



43 **44**

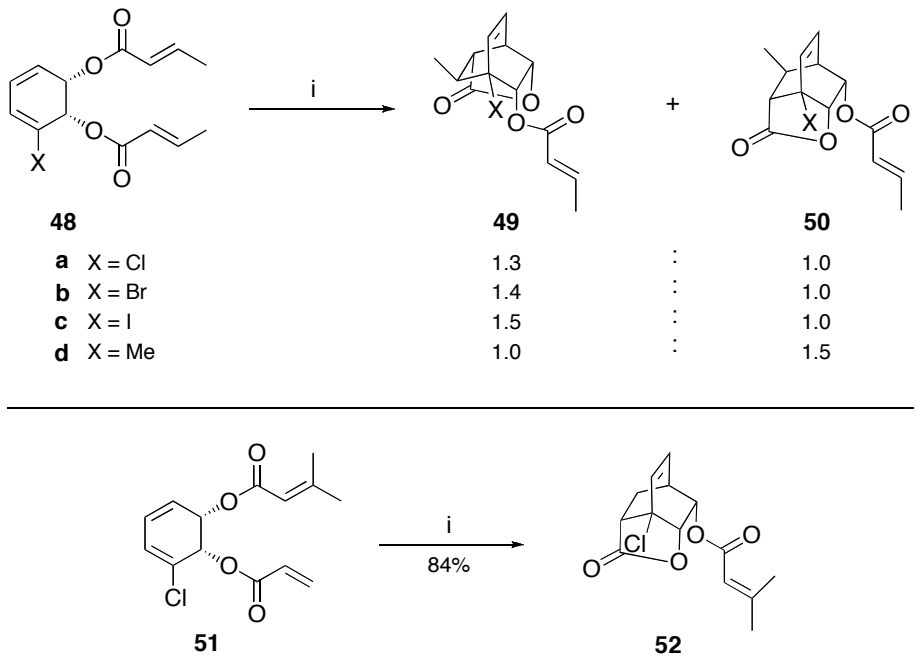


46 **45** **47**

Scheme 1.8: *Reagents and conditions* (i) benzene, 110 ºC (sealed tube), 15 h; (ii) CCl_4, 77 ºC, 7 h.

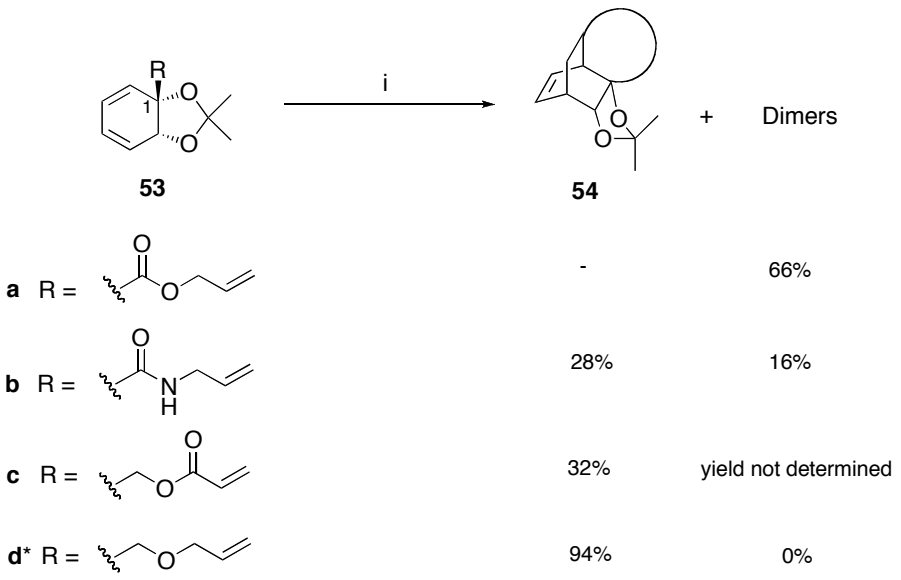
In each of these examples, there are two diene moieties and, as a consequence, two regiochemical outcomes are possible. In both cases it was found that the endocyclic diene of the *c*-DHC participates as the 4π-cycloaddend affording a single cycloadduct. In these instances the facial selectivity of the IMDA reaction is constrained by the pre-existing stereocentre to which the dienophile is attached.

In an extension of this type of work Banwell *et al*. investigated the IMDA reactions of *c*-DHC derivatives possessing two potentially dienophilic residues, one attached at each hydroxyl group of the *c*-DHC core (Scheme 1.9).[32] As in the previous cases, two regiochemical outcomes are possible for the cycloaddition reactions of compounds of this type. In the event, it was found that, depending on the tetraene precursor (**48a** to **48d**), varying mixtures of cycloadducts **49** and **50** were obtained (Scheme 1.9). The selectivity of the reaction was observed to be sensitive to steric effects with the proportion of cycloadduct **49** (in which the dienophile furtherest from the C3 substituent has engaged in the cycloaddition) increasing as the size of X increases. The IMDA reactions of mixed diesters, such as **51**, were also investigated. These studies revealed that the nature of the substituents on the dienophile have a greater effect on the regioselectivity of these processes than the substituents on the diene (X), with cycloadduct **52** being the only isolable product of the IMDA reaction of tetraene **51**.



Scheme 1.9: *Reagents and conditions* (i) toluene, reflux, various times.

Mihovilovic *et al*. have investigated the IMDA reactions of *c*-DHC derivatives possessing various dienophilic tethers attached at C1 of the *c*-DHC framework (Scheme 1.10).[33] In these examples, the dienophilic moieties were attached *via* ester (**53a** and **53c**), amide (**53b**) or ether (**53d**) linkages and the diol moiety was protected as the corresponding acetonide in order to increase the thermal stability of the conjugates.

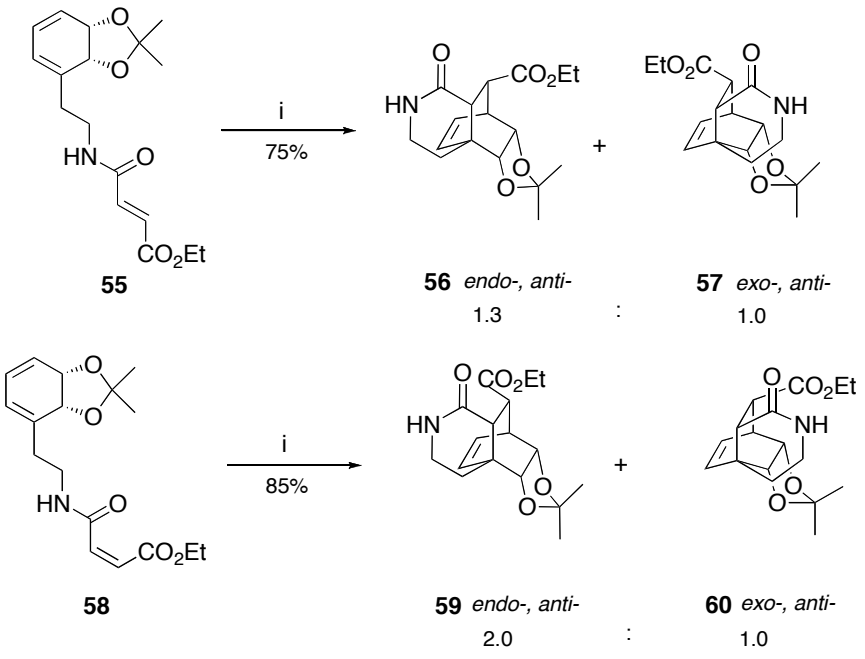


Scheme 1.10: *Reagents and conditions* (i) microwave, 210 ºC, 500 min (*135 ºC, 200 min).

The IMDA reactions of these substrates were found to occur in competition with a dimerisation reaction. In particular, significant quantities of dimeric compounds were obtained during the reactions of substrates possessing ether or amide linkages. Surprisingly, although the dienophile of the allyl ether derivative **53d** represents the least activated double bond of all the precursors, the IMDA reaction of this substrate was found to be the most efficient, giving an almost quantitative yield of the desired product. As this substrate represents the most flexible system used in the study, the authors concluded that conformational flexibility plays a significant role in reactions of this type.[33]

Hudlicky and co-workers reported the first examples of IMDA reactions of *c*-DHC derivatives in which the dienophile was not tethered to the diene *via* a stereogenic centre (Scheme 1.11).[34] This allowed investigation of the diasterio- and facial-selectivities associated with such reactions. When trienes **55** and **58** were heated at reflux in benzene, a mixture of two cycloadducts was obtained in each case. Following extensive NMR analysis, it was determined that, in both instances, the IMDA reaction had occurred with excellent facial selectivity, involving exclusive reaction at the face opposite the acetonide moiety (*anti*-addition). However,

as is common for the intramolecular variant of the Diels-Alder reaction, only moderate diastereoselectivity was observed with both *endo*- and *exo*-isomers being formed.❖



Scheme 1.11: *Reagents and conditions* (i) benzene, reflux.

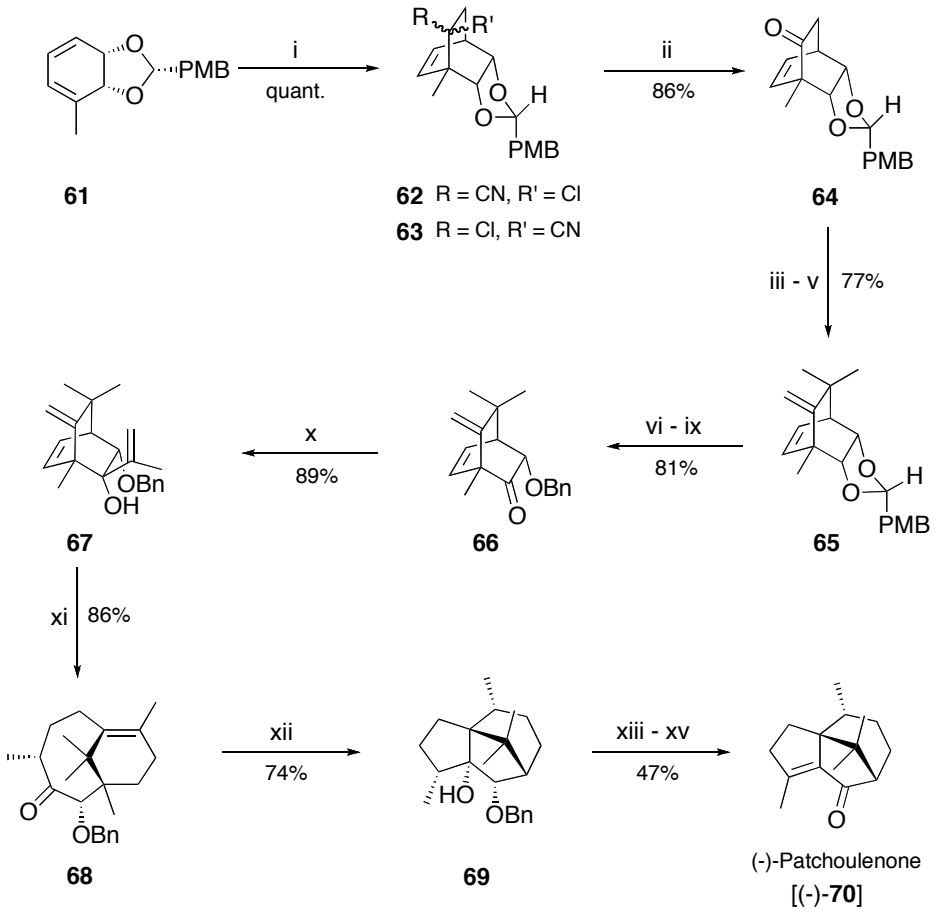
1.3 *cis*-1,2-Dihydrocatechols and Diels-Alder Cycloaddition Reactions in Natural Product Synthesis

The cycloadducts produced *via* the Diels-Alder cycloaddition reactions of *c*-DHC derivatives are enantiopure and possess multiple functionalities. As such they can often serve as highly valuable intermediates in total synthesis. As a result, this reaction has been exploited in enantioselective syntheses of a wide range of natural product frameworks.[35-43] The following Section provides accounts of two such syntheses: Banwell's synthesis of (-)-patchoulenone [(-)-**70**],[44] which utilises an *inter*molecular Diels-Alder cycloaddition reaction and Hudlicky's synthesis of (-)-zeylena [(-)-**76**],[30] which employs the *intra*molecular variant. Both of these syntheses rely on a stereoselective Diels-Alder reaction in order to generate the stereochemistry required for the target natural products. A particular emphasis is placed on the methods by which this stereoselectivity is achieved.

❖ *Endo*- and *exo*-assignments of these cycloadducts are based on the configuration of the amide carbonyl group in the transition state leading to the products.

Banwell's synthesis of (-)-patchoulenone (2003)

The synthesis of the sesquiterpenoid natural product (-)-patchoulenone[38] (Scheme 1.12) commences with *endo*-PMB acetal **61** (derived from *c*-DHC **35**), which was reacted with α-chloroacrylonitrile in a thermally promoted Diels-Alder reaction. The steric bulk imparted by the acetal protecting group ensured that the cycloaddition reaction occurred with complete facial selectivity, while the regioselectively was governed by the "*ortho* effect", to afford, exclusively, the *anti*-, *ortho*-adducts. This stereochemical outcome ensured the correct stereochemistry was established for successful completion of the synthesis of the title natural product. While the diastereoselectivity was lower (a 4:1 mixture of *endo*- and *exo*-cycloadducts, **62** and **63** respectively, was obtained) this was of little consequence as base-promoted hydrolysis of the mixture resulted in formation of a single ketone derivative **64**.

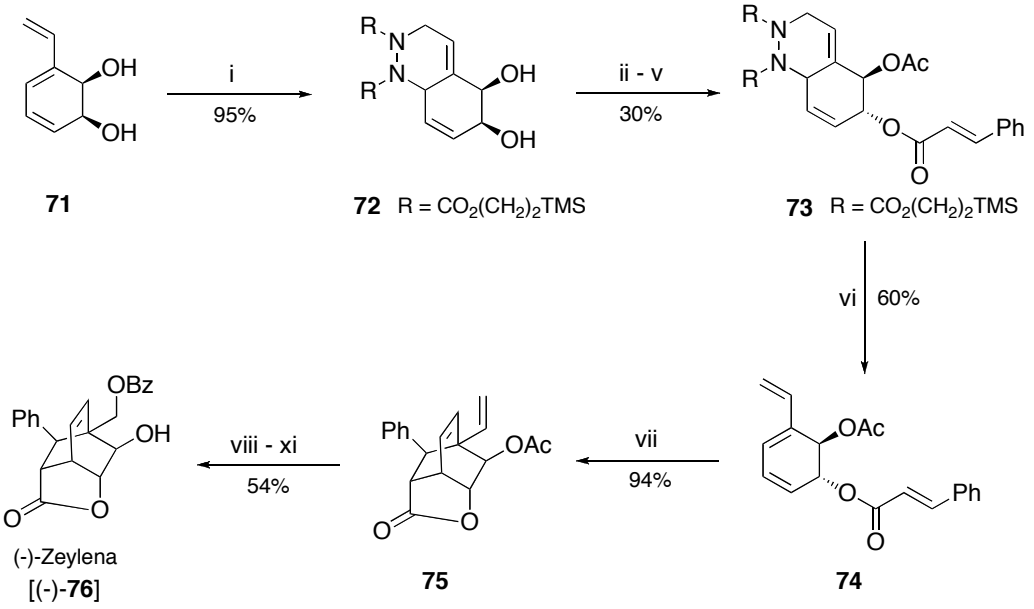


Scheme 1.12: *Reagents* (i) α-chloroacrylonitrile; (ii) KOH, *t*-BuOH; (iii) NaHMDS, MeI; (iv) Pt_2O, H_2; (v) $Ph_3P{=}CH_2$; (vi) DIBAL-H; (vii) NaH, BnBr, Bu_4NI; (viii) DDQ; (ix) TPAP, NMO; (x) isoproprenyl lithium; (xi) NaH, 66 ºC; (xii) PhSH, SmI_2; (xiii) 10 % Pd on C, H_2; (xiv) SO_3/pyridine; (xv) $SOCl_2$, pyridine.

gem-Dimethylation of ketone **64** followed by hydrogenation of the double bond and Wittig olefination to install the exocyclic methylene unit afforded compound **65**. Manipulation of the PMB acetal moiety within substrate **65** *via* standard procedures then led, over four steps, to ketone **66,** which was subsequently reacted with isoprenyl lithium to afford dienol **67** in a completely diastereoselective manner.[44] 1,5-Dienols such as compound **67** participate in anionic oxy-Cope rearrangements to afford the corresponding bicyclo[5.3.1]undecanone systems. Thus, treatment of compound **67** with sodium hydride in refluxing THF afforded ketone **68**, which then underwent a reductive cyclisation in the presence of samarium diiodide and thiophenol to afford alcohol **69**. With the desired tricyclic framework in place, standard functional group manipulations allowed for conversion of compound **69** into (-)-patchoulenone [(-)-**70**].

Hudlicky's synthesis of (-)-zeylena (1989)

Hudlicky and co-workers' total synthesis of (-)-zeylena [(-)-**76**] (Scheme 1.13) is the only one reported to date that exploits the *intra*molecular Diels-Alder reaction of a *c*-DHC derivative.[30] This cycloaddition reaction is proposed to mimic the biogenesis of both (-)-zeylena and other natural products possessing frameworks of this type.

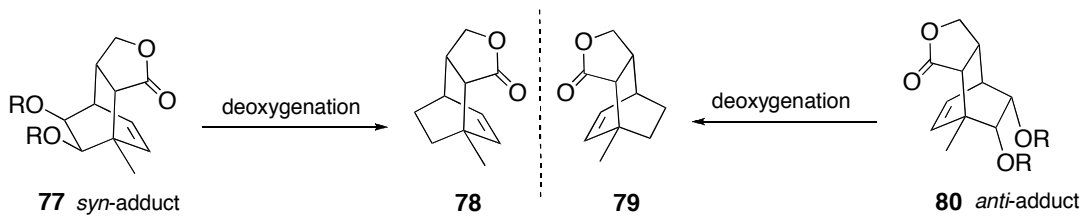


Scheme 1.13: *Reagents* (i) bis-(2,2,2-trichloroethyl)azodicarboxylate; (ii) THSCl, imidazole; (iii) Ac_2O, pyridine; (iv) TBAF; (v) PPh_3, DEAD, cinnamic acid; (vi) Zn-Cu couple, AcOH; (vii) benzene, 110 ºC; (viii) a) O_3; b) DMS; (ix) $NaBH_4$; (x) benzoic acid, isobutyl chloroformate, Et_3N; (xi) *p*-TsOH•H_2O.

Starting with *c*-DHC **71**, which is derived from the microbial oxidation of styrene, the first part of the synthesis involved inversion of the C1 alcohol. To this end, the starting material was first reacted with the bis-(2,2,2-trichloroethyl) azodicarboxylate (TEAD) to afford cycloadduct **72**. Protection of the diene moiety in this manner was necessary to avoid aromatisation of the *c*-DHC during the subsequent reactions. Compound **72** was then acylated selectively at the C2-hydroxyl, *via* a 3-step process, and Mitsunobu inversion of the resulting alcohol then afforded cinnamate **73.** Thermally-induced cycloreversion of compound **73** afforded tetraene **74**, the substrate for the key IMDA reaction. As anticipated, tetraene **74** underwent a thermally-induced intramolecular Diels–Alder reaction to afford cycloadduct **75** as the exclusive product of the reaction. The stereoselectivity of this process can be attributed to the conformational constraints imposed at the transition state by the short connecting tether and the pre-existing stereocentre to which the dienophile is attached. With the synthesis of the core structure complete, compound **75** was readily converted into (-)-zeylena [(-)-**76**] using standard procedures.[45]

1.4 Enantiodivergent syntheses: Exploiting the Facial Selectivity of the Diels-Alder Cycloadditions of *cis*-1,2-Dihydrocatechols

As described in Section 1.1, one criticism of the use of enzymatically derived *c*-DHCs as enantiopure starting materials in total synthesis is that, in most cases, only one enantiomer can be accessed. This would thus seem to limit the user to a single enantiomeric form of any target compound, and has often resulted in sole access to the unnatural enantiomeric series of a given natural product.[46,47] However, it is possible that this limitation could be overcome by using the combination of the microbial-oxidation and Diels-Alder cycloaddition reactions described in this Chapter. This is because the *syn*- and *anti*-adducts produced *via* the Diels-Alder cycloadditions of *c*-DHC derivatives are pseudo-enantiomeric (Scheme 1.14). As a result, synthesis of either enantiomeric form of the Diels-Alder adduct from a single enantiopure starting material is possible if the facial selectivity of the Diels-Alder reaction can be controlled.



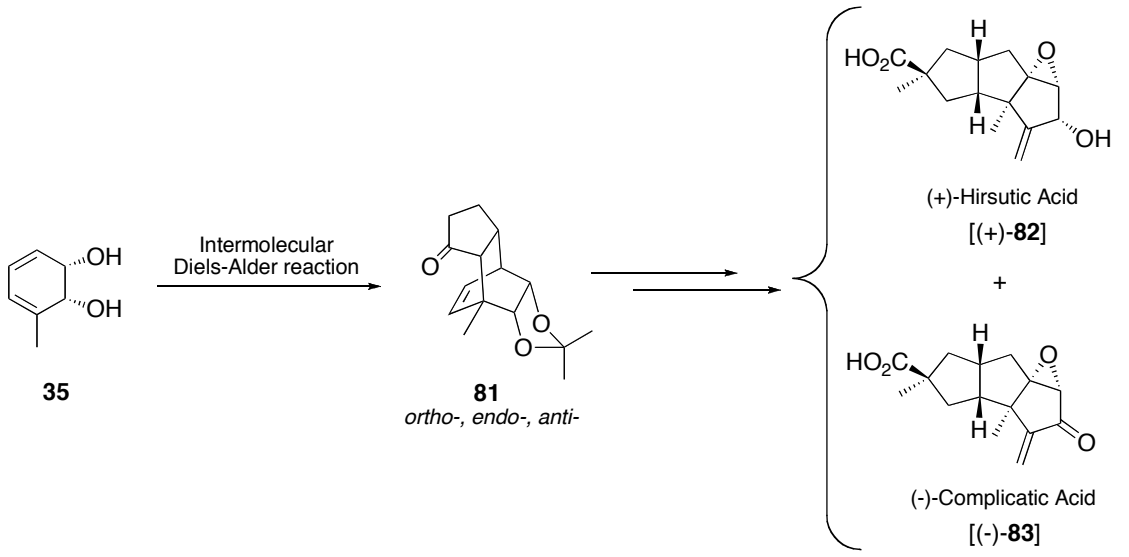
77 *syn*-adduct **78** **79** **80** *anti*-adduct

Scheme 1.14: *Pseudo-enantiomeric relationship between the* syn- *and* anti-*adducts produced during the Diels-Alder cycloaddition reactions of c-DHC derivatives.*

1.5 Overview of the Research Described in this Thesis

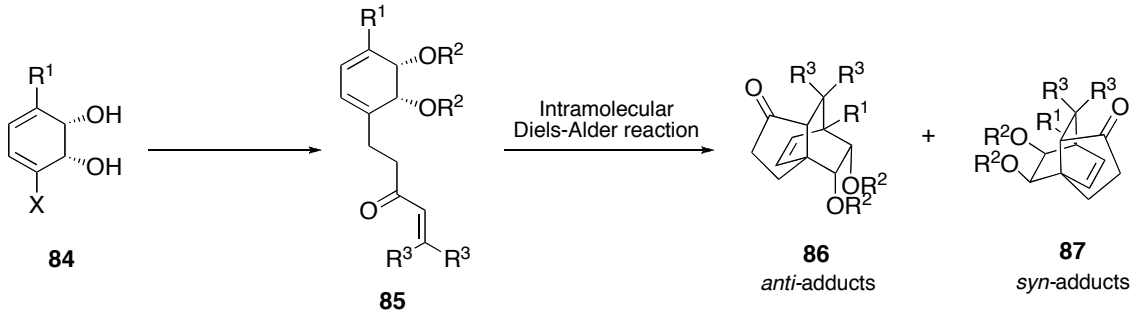
The work described in this Thesis was undertaken with the aim of exploring and expanding upon the versatility of the enzymatic oxidation and Diels-Alder reaction sequence, described in this Chapter, for the purposes of synthesising a structurally diverse range of biologically active natural products.

Chapter Two describes the application of an *inter*molecular Diels-Alder cycloaddition reaction in the total synthesis of the linear triquinane type natural products (+)-hirsutic acid [(+)-**82**] and (-)-complicatic acid [(-)-**83**] (Scheme 1.15). This approach exploits strategies that have been developed in the Banwell group, involving a Diels-Alder reaction and subsequent photochemical rearrangement as the key steps for the stereoselective generation of *cis:anti:cis* fused linear triquinane frameworks. However, while the previous work utilised a *syn*-selective Diels-Alder cycloaddition reaction for the synthesis of the non-natural enantiomer of the simple triquinane *ent*-(-)-hirsutene,[42,43] the syntheses of targets (+)-**82** and (-)-**83** employ an *anti*-selective Diels-Alder reaction to access the natural enantiomeric series of these more complex natural products. Thus, the successful completion of total syntheses of these target compounds not only demonstrates an effective application of the enzymatic oxidation/Diels-Alder reaction sequence but also supports the proposal that, by controlling the facial selectivity of the Diels–Alder reactions involving *c*-DHC derivatives, either enantiomeric form of a target natural product can be accessed.



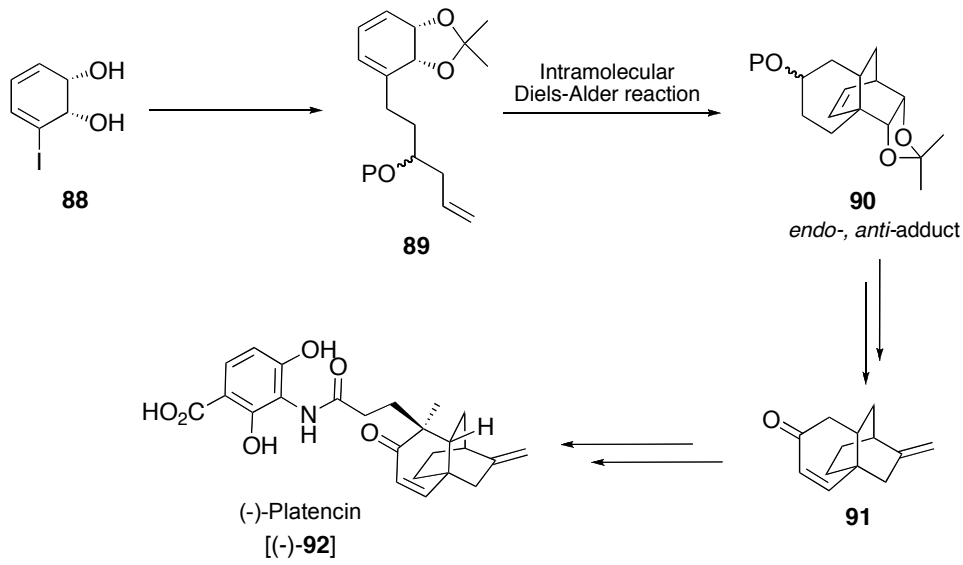
Scheme 1.15: *Outline of the work described in Chapter Two.*

Chapter Three describes the first systematic study of the stereoselectivities associated with the *intra*molecular Diels-Alder reactions of *c*-DHC derivatives. It also details the syntheses of several novel *c*-DHC derivatives of the general type **85** and their participation in IMDA cycloaddition reactions to generate cycloadducts **86** and **87** (Scheme 1.16). The results of investigations into the effects of various substitution patterns (varying R^1, R^3 and R^4) and diol protecting groups (R^2) on the facial selectivity of the reaction are also presented.



Scheme 1.16: *Outline of the work described in Chapter Three.*

Chapter Four describes the formal total synthesis of the novel and potent antibacterial agent (-)-platencin [(-)-**92**] (Scheme 1.17). This strategy draws and expands upon the chemistries described in Chapter Three. Thus, *c*-DHC derivative **89** undergoes a stereoselective IMDA reaction to afford cycloadduct **90**, possessing the correct stereochemistry for the target natural product. The elaboration of cycloadduct **90** into enone **91**, which has been converted into (-)-platencin [(-)-**92**] by a number of groups,[48,49] is then described.



Scheme 1.16: *Outline of work undertaken in Chapter Four.*

In summary, this Thesis presents the results of an extended investigation into the value of employing *c*-DHC derivatives in facially selective Diels-Alder reactions. The utility of these processes in natural product synthesis is highlighted through the preparations of (+)-hirsutic acid, (-)-complicatic acid and (-)-platencin.

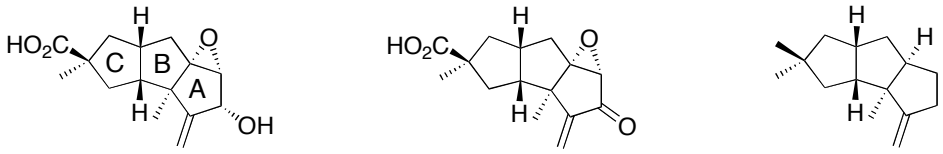
CHAPTER TWO

Total Syntheses of (+)-Hirsutic Acid and (-)-Complicatic Acid

2.1 Introduction

2.1.1 Isolation and characterisation of (+)-hirsutic acid and (-)-complicatic acid

In 1947 Heatley *et al*. reported the isolation of two linear triquinoid natural products, hirsutic acid [(+)-**82**] and hirsutic acid N, from the basidiomycete *Stereum hirsutum*.[50] Although the molecular formula of hirsutic acid was determined at this time its structure and absolute configuration were not established until 1967 when an X-ray crystal structure was obtained by Comer *et al.*[51-53] Some controversy remains regarding the identity of the basidiomycete from which hirsutic acid and hirsutic acid N were isolated. In fact, nobody other than Heatley *et al*. has been able to isolate hirsutic acid from *S. hirsutum*.[53] In 1973, however, Mellows and Mantle were able to isolate and characterise (+)-hirsutic acid along with the related sequiterpenoid (-)-complicatic acid [(-)-**83**] from *S. complicatum*.[54] Furthermore, Mellows and Mantle proposed that hirsutic acid N was in fact (-)-complicatic acid.



(+)-Hirsutic Acid [(+)-**82**] | (-)-Complicatic Acid [(-)-**83**] | (+)-Hirsutene [(+)-**84**]

Figure 2.1: *Target compounds (+)-hirsutic acid and (-)-complicatic acid and their proposed biogenetic precursor (+)-hirsutene.*

Unlike (+)-hirsutic acid, which is not biologically active,[50] (-)-complicatic acid displays activity against a range of Gram-positive and Gram-negative bacteria as well as certain fungi.[54,55] (-)-Complicatic acid is also mutagenic, as determined by the Ames test.[55] The observed antibacterial and mutagenic activity is most likely a consequence of the compound's ability to

conjugate with the amino acid cysteine *via* the α,β-unsaturated ketone moiety. Indeed, it has been proposed that (+)-hirsutic acid is an inactive precursor that is oxidised, at certain stages of growth of the producing organism, to biologically active (-)-complicatic acid.[50,54]

(+)-Hirsutene [(+)-**93**] (Figure 2.1) is thought to be the biogenetic precursor to the entire linear triquinane class of sesquiterpenes, including acids **82** and **83**.[56] It was first identified as a metabolite of the basidiomycete *Coriolis consors*, and is believed to be generated *in vivo*, *via* cation-mediated cyclization processes, from the monocyclic and polyunsaturated sesquiterpene humulene.[57]

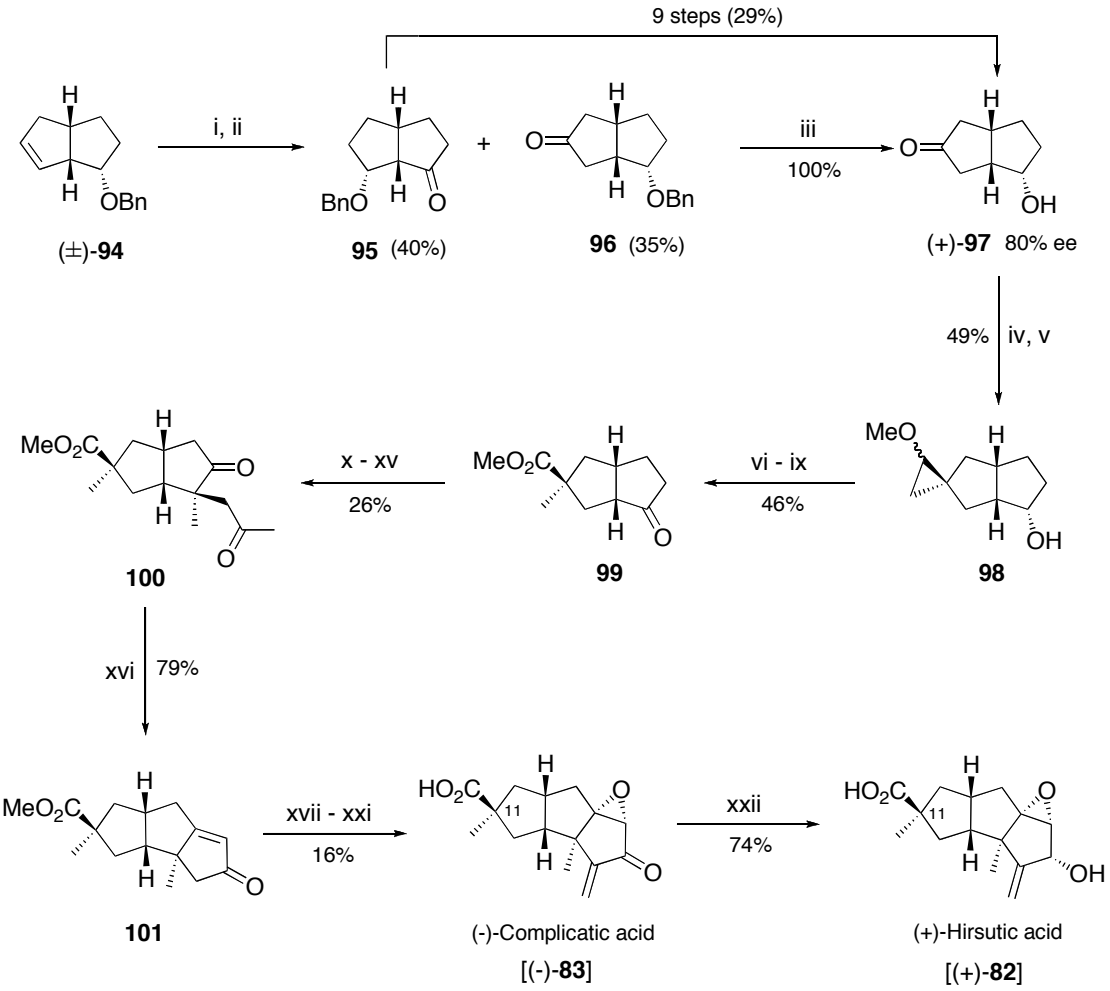
2.1.2 Previous studies on the synthesis (+)-hirsutic acid and (-)-complicatic acid

The title natural products have each been the subject of a number of synthetic endeavours. Preliminary studies were reported in the early 1970's by Matsumoto *et al.*[58] and Lansbury *et al*.[59,60] These were quickly followed by the first total synthesis of (±)-complicatic acid [(±)-**83**].[61] At this time it was also shown that (±)-complicatic acid could be selectively reduced to (±)-hirsutic acid using sodium borohydride. Subsequently, six total[62-64] or formal total[58,65-69] syntheses of acids (±)-**82** and (±)-**83**, along with two asymmetric syntheses,[70,71] have been reported.

The following Section provides summaries of these total syntheses. Thus, both of the aforementioned enantioselective syntheses are described below, along with two syntheses of racemic material that are particularly relevant to the work detailed in this Thesis.

Ikegami's asymmetric syntheses of (+)-hirsutic acid and (-)-complicatic acid (1982)

The first enantioselective total syntheses of (-)-complicatic acid and (+)-hirsutic acid were reported by Ikegami *et al.* in 1982 (Scheme 2.1).[70,72] These began with the development of an asymmetric route to hydroxy ketone **2.7**, a key intermediate in the synthesis of (±)-hirsutic acid that they had published in 1981.[65] So, asymmetric hydroboration of olefin (±)-**94** with (+)-di-3-pinanylborane afforded, after oxidation with alkaline hydrogen peroxide, an inseparable mixture of enantiopure alcohols. PCC-mediated oxidation of this mixture gave ketones **95** and **96**, both of which were ultimately converted into hydroxy ketone (+)-**97**.



Scheme 2.1: *Reagents* (i) a) (+)-di-3-pinanylborane; b) H_2O_2, NaOH; (ii) PCC; (iii) 5% Pd on C, H_2; (iv) Ph_3P=CHOMe; (v) Zn-Cu couple, I_2 (cat.); (vi) PCC; (vii) HCl, MeOH; (viii) Jones reagent; (ix) CH_2N_2; (x) MeLi; (xi) $K_2S_2O_7$; (xii) borane-THF; (xiii) PCC; (xiv) NaH, allyl bromide; (xv) $PdCl_2$, CuCl, O_2; (xvi) *t*-BuOK, *t*-BuOH; (xvii) LDA, MeI; (xviii) LDA, phenylselenyl bromide; (xix) H_2O_2, AcOH; (xx) LiI, DMF; (xxi) H_2O_2, NaOH; (xxii) $NaBH_4$.

Wittig olefination of compound (+)-**97** with (methoxymethylene)triphenyl phosphorane, followed by a stereoselective Simmons-Smith reaction, yielded cyclopropane **98** incorporating the desired stereochemistry at the newly formed quaternary centre. Compound **98** was then submitted to a series of functional group manipulations to reveal the methyl ester and methyl groups of compound **99** as required at C11 of the natural product.

Ketone **99** was subjected to a series of reactions that ultimately resulted in a 1,2-transposition of the carbonyl moiety as well as stereo- and regio-specific installation of the quaternary centre alpha to the ketone. This sequence proceeded *via* an allyl-ketone that was oxidised to

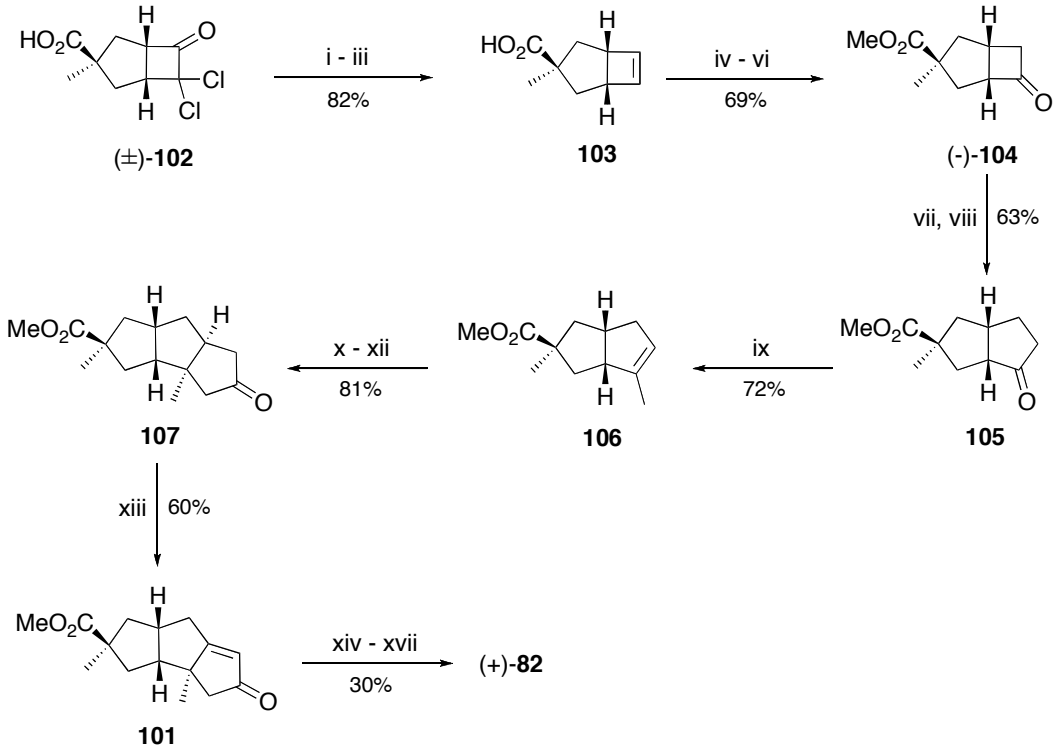
1,4-diketone **100** under Wacker oxidation conditions. Intramolecular aldol condensation of compound **100** resulted in the formation of the final five-membered ring of triquinane **101**, a key intermediate of Ikegami's previously reported synthesis of (±)-hirsutic acid.[66]

The closing stages of the synthesis involved introduction of the α-methylene functionality *via* the formation and subsequent elimination of a phenyl selenide residue. This was followed by cleavage of the methyl ester. Finally, using the protocols of Matsumoto *et al*.,[61] regio- and stereo-selective epoxidation of the endocyclic double bond afforded (-)-complicatic acid [(-)-**83**], which was selectively converted into (+)-hirsutic acid [(+)-**82**] *via* reduction of the former material with sodium borohydride.

Greene's asymmetric synthesis of (+)-hirsutic acid (1985)

Greene *et al.* published their enantioselective synthesis of (+)-hirsutic acid in 1985 (Scheme 2.2).[71] As with the work of Ikegami and co-workers, this synthesis was an extension of a synthesis of racemic hirsutic acid that they had published in 1983.[63] The key step is an iterative, three-carbon annulation protocol that was developed to allow for the construction of complex, fused polycyclopentanoid skeleta. Greene and co-workers initially envisioned that an asymmetric synthesis could be achieved simply by resolution of keto-acid **102**, a key intermediate in their synthesis of (±)-hirsutic acid. However, although resolution was examined with various chiral amines, the results were disappointing and an alternative route was developed involving asymmetric hydroboration of the ester of *meso*-acid **103**. The synthesis of compound **103** was readily achieved in three steps from keto-acid **102** and in 82% overall yield.

Acid **103** was protected as the corresponding methyl ester and this was subjected to asymmetric hydroboration using (+)-di-*iso*-pinocampheylborane. Alkaline hydrogen peroxide-mediated oxidation to the corresponding alcohol followed by Collins oxidation then afforded cyclobutanone (-)-**104** in 92% ee. Regioselective ring-expansion was achieved by exposure of compound **104** to ethyl diazoacetate and antimony pentachloride. This yielded the desired β-keto-ester, which underwent smooth decarboethoxylation on heating to afford diquinane **105**. A one-pot methylation/dehydrogenation procedure gave cyclopentene **106**, the substrate for the key three-carbon annulation protocol. So, using previously defined conditions,[71] a stereo- and regio-selective cycloaddition reaction was performed between olefin **106** and dichloroketene to afford the expected cyclobutanone. Subsequent diazomethane-mediated ring expansion then gave the required triquinane framework. Finally, zinc-mediated dechlorination afforded the *cis:anti:cis* fused linear triquinoid intermediate **107**.



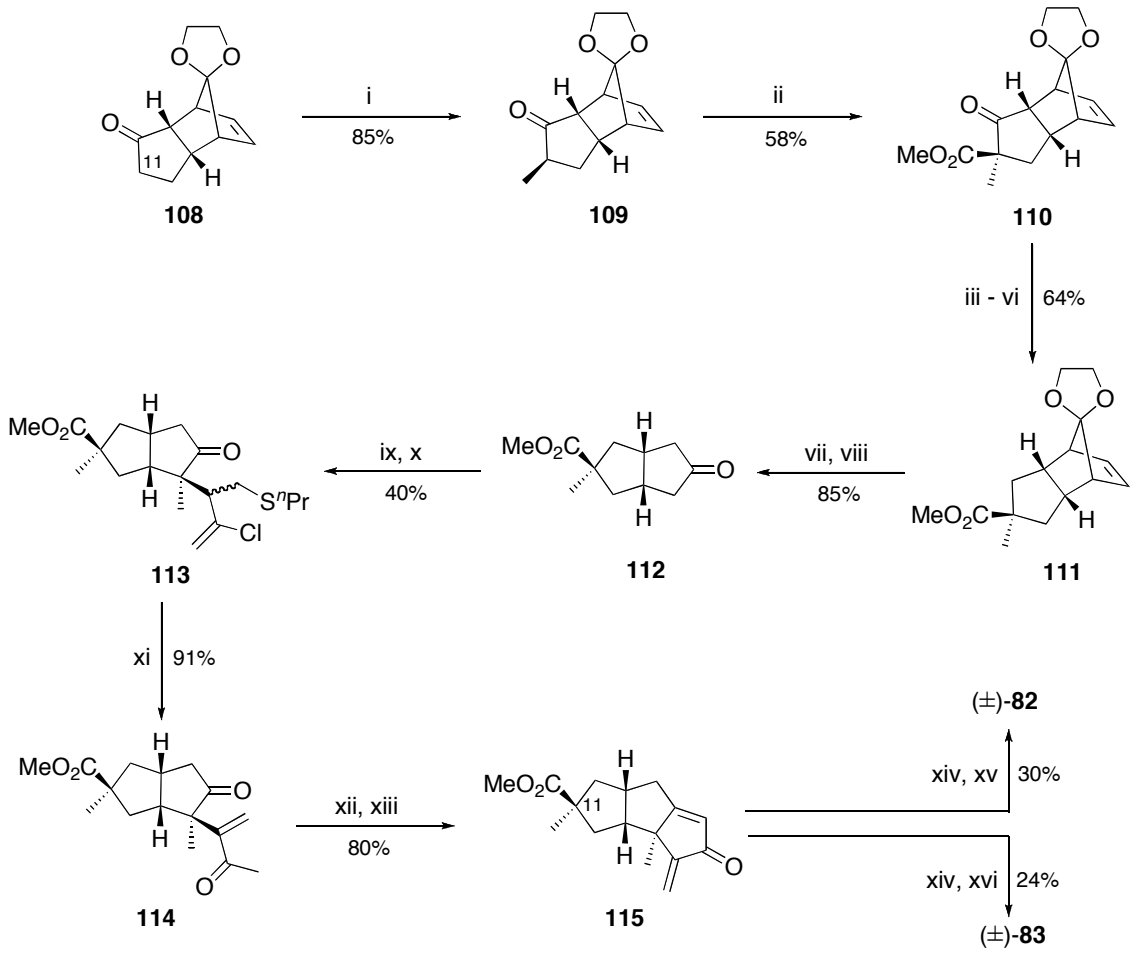
Scheme 2.2: *Reagents* (i) $NaBH_4$; (ii) CH_3SO_2Cl, Et_3N; (iii) Na, NH_3; (iv) CH_2N_2; (v) a) (+)-di-*iso*-pinocampheylborane; b) H_2O_2, NaOH; (vi) Collins reagent; (vii) $SbCl_5$, ethyl diazoacetate; (viii) DME, H_2O, reflux; (ix) a) CH_3MgBr; b) $HClO_4$, H_2O; (x) Zn-Cu couple, CCl_3COCl, $POCl_3$; (xi) CH_2N_2; (xii) Zn, AcOH; (xiii) $PdCl_2$, $Pd(OAc)_2$; (xiv) tetrahydrothiophene, $AlBr_3$; (xv) LiHMDS, HCO_2CH_3; (xvi) K_2CO_3, acetone; (xvii) a) H_2O_2, NaOH; b) $NaBH_4$.

Elaboration of triquinane **107** to (+)-hirsutic acid was achieved in six steps. Thus, palladium(II)-mediated oxidation of this compound afforded Ikegami's enone **101**,[70] the ester moiety of which was cleaved, by treatment with aluminium bromide and thiophene, to give the corresponding carboxylic acid. The required exocyclic methylene was introduced *via* the corresponding hydroxymethylene derivative and the nucleophilic epoxidation reaction proceeded as previously described[61] to provide (-)-complicatic acid which could be reduced, *in situ* with sodium borohydride, to (+)-hirsutic acid [(+)-**82**].

Schuda's total syntheses of (±)-complicatic and hirsutic acids (1986)

Much of Schuda and co-workers 1986 account of their synthesis of complicatic and hirsutic acids[64] was concerned with stereoselective introduction of the C11 quaternary centre as this was noted, by the group, to be a recurring problem encountered in previous syntheses. Their

approach employed a rigid tricyclic ring structure to control the assembly of the C11 centre after which, cleavage of one of the rings revealed a diquinane intermediate (Scheme 2.3).



Scheme 2.3: *Reagents* (i) LDA, MeI; (ii) KHMDS, $NCCO_2Me$; (iii) $NaBH_4$; (iv) $(CF_3SO_2)_2O$, pyridine; (v) NaI, acetone; (vi) Zn, DME; (vii) $RuO_2{\bullet}H_2O$, $NaIO_4$; (viii) HCl; (ix) LDA, MeI; (x) a) $CH(OMe)_3$, *p*-TsOH; b) 2-chloro-4-(propylthio)-2-buten-1-ol; c) 165 ºC; (xi) $Hg(OAc)_2$, HCO_2H, HCO_2NH_4; (xii) *t*-BuOK, *t*-BuOH; (xiii) *p*-TsOH; (xiv) LiI, DMF; (xv) a) H_2O_2, NaOH; b) $NaBH_4$; (xvi) H_2O_2, $NaHCO_3$.

Thus, starting from compound **108** (synthesised in five steps from ketal-protected cyclopentanone) it was anticipated that alkylation of the C11 enolate would occur from the *exo*-face of the molecule. The desired relative stereochemistry could therefore be installed by firstly introducing the methyl group followed by the carboxyl-derived functionality. To this end, treatment of compound **108** with lithium diisopropylamide (LDA) followed by the addition of methyl iodide gave the predicted *exo*-methylated ketone (**109**) as the sole product of the reaction. Introduction of the carboxyl functionality proved problematic due to formation of the undesired regioisomeric enolate from ketone **109** and *O*- rather than *C*-alkylation. Following a

series of enolate trapping experiments, it was established that treatment of ketone **109** with KHMDS and methyl cyanoformate provided ester **110** in 58% yield. However, concomitant formation of the corresponding enol carbonate could not be avoided so this material was recycled to methyl ketone **109** by treatment with potassium carbonate in MeOH.

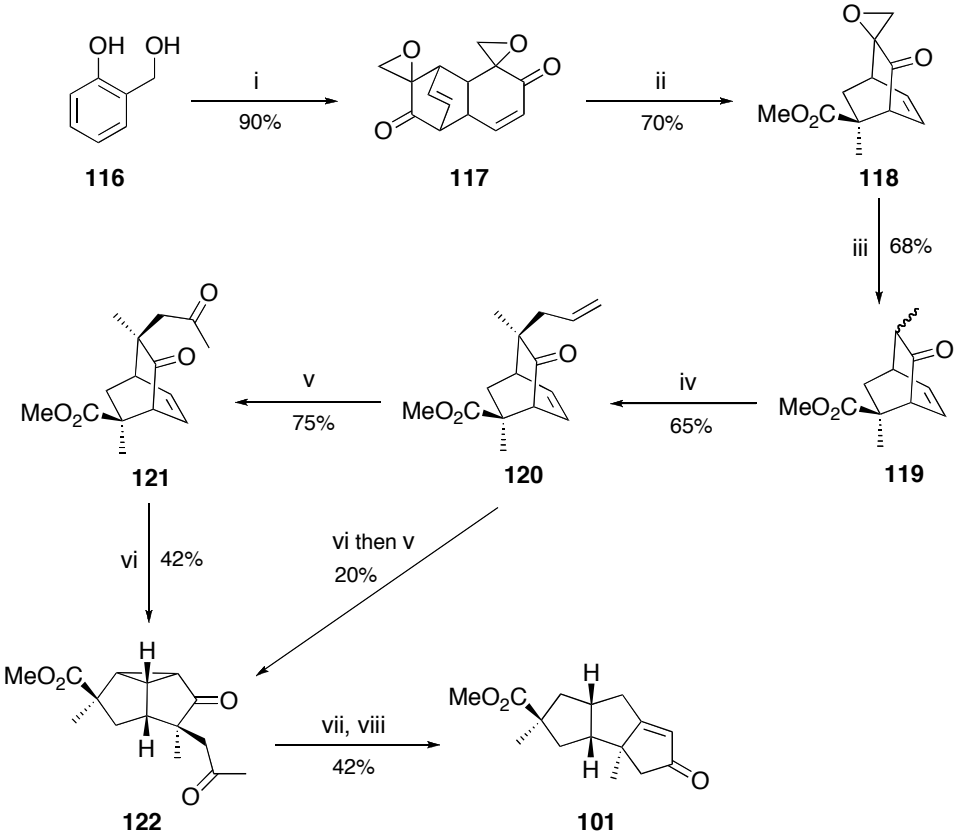
Deoxygenation of compound **110** was achieved *via* a four-step reaction sequence involving reduction of the carbonyl moiety, conversion of the corresponding alcohol into the iodide (*via* the tosylate), and deiodination using zinc in DME/MeOH to yield compound **111** in 57% overall yield from β-keto-ester **110**. Oxidative cleavage of the norbornene double bond with ruthenium tetroxide followed by acid-catalysed hydrolysis of the acetal and concomitant bisdecarboxylation then furnished diquinane **112**.

The final stages of the synthesis required annulation of the third five-membered ring onto diquinane **112**. To these ends, alkylation with methyl iodide then 2-chloro-4-(propylthio)-2-buten-1-ol and followed by a ketal-Claisen rearrangement allowed stereoselective installation of the second quaternary centre yielding compound **113**. Hydrolysis-elimination of the side chain followed by intramolecular aldol condensation afforded the linear triquinoid intermediate **115** that was converted, using previously described protocols,[61] into (±)-hirsutic acid and (±)-complicatic acid.

Singh's formal total syntheses of (±)-complicatic and hirsutic acids (2004 and 2007)

The formal total synthesis of (±)-hirsutic acid reported by Singh *et al.* in 2004[68] (Scheme 2.4) resembles the approach described in this Thesis by virtue of incorporating both a Diels-Alder cycloaddition reaction and a photochemical rearrangement process as key steps. So, this synthesis commenced with the oxidation of the readily available salicyl alcohol (**116**) with aqueous sodium metaperiodate to give epoxy dimer **117**. Pyrolysis of the dimer afforded the corresponding diene which then underwent a Diels-Alder reaction with methyl methacrylate to afford compound **118**.[69] Deoxygenation of the oxirane ring using zinc in dioxane furnished methyl ketone **119** as a mixture of epimers. Alkylation of this mixture proceeded stereoselectively with allyl bromide to give allyl ketone **120** that was readily oxidised, using a Wacker protocol, to 1,4-diketone **121**. Compounds **120** and **121** were both subjected to triplet sensitised, photochemically-induced oxa-di-π-methane rearrangements because this process is known to be sensitive to the functional groups appended to the bicyclic system and because either of the corresponding products could be elaborated to the natural product. In the event, it was found that the reaction proceeded more efficiently when compound **121** (42%) rather than congener **120** (30%) was used as the photo-substrate. This was attributed to competitive absorption of the light by the olefinic group present in the allylic chain of compound **120**.

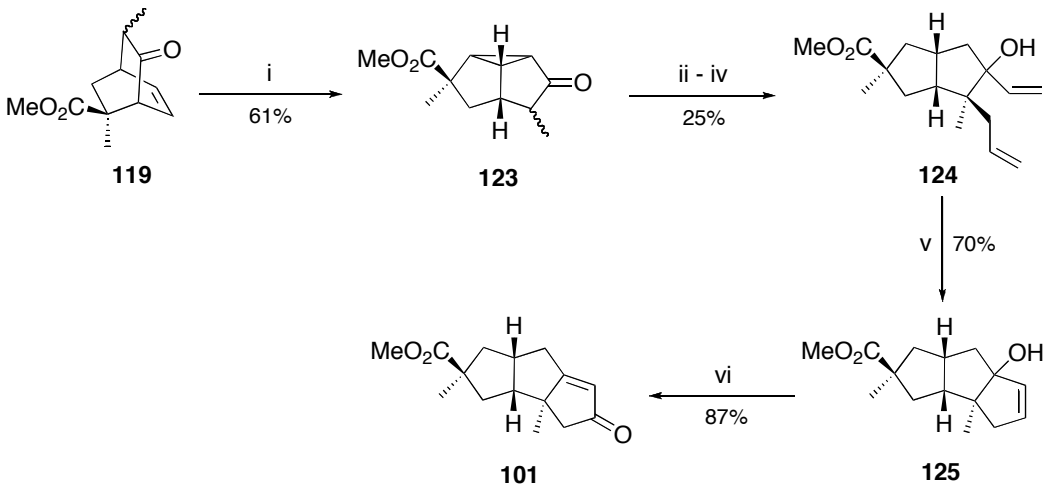
Treatment of diquinane **122** with tri-*n*-butyltin hydride and 2,2-azobis*iso*butyronitrile (AIBN) selectively cleaved the peripheral cyclopropane bond and a subsequent base-induced intramolecular aldol condensation afforded the linear tricyclopentanoid **101**. As compound **101** had already been converted into both complicatic and hirsutic acids its acquisition represented a formal total synthesis of the target natural products.



Scheme 2.4: *Reagents* (i) aq. $NaIO_4$; (ii) methyl methacrylate; (iii) Zn, NH_4Cl; (iv) NaH, allyl bromide; (v) $PdCl_2$, CuCl, O_2; (vi) hν, acetone; (vii) tri-*n*-butyltin hydride, AIBN; (viii) *t*-BuOK, *t*-BuOH.

In 2007 Singh *et al.* reported an alternative route to triquinane **101** (Scheme 2.5) in an attempt to avoid the problem of the low yielding oxa-di-π-methane rearrangements of bicyclic compounds **120** and **121**.[69] Thus, they proposed that methyl ketone **119** would undergo the required photoreaction with better efficiency since it contains only the β,γ-enone chromophore and that the anticipated photoproduct would be readily elaborated, *via* a ring-closing metathesis, so as to allow installation of the third ring. Accordingly, β,γ-enone **119** was irradiated under triplet-sensitised conditions to give diquinane **123** in 61% yield. Reductive cleavage of the cyclopropane ring was followed by stereoselective installation of two olefinic chains to afford **124**. Ring-closing metathesis of this last compound using Grubb's second-generation catalyst

followed by PCC oxidation furnished intermediate **101**, the acquisition of which represents a formal synthesis of (±)-complicatic and hirsutic acids.



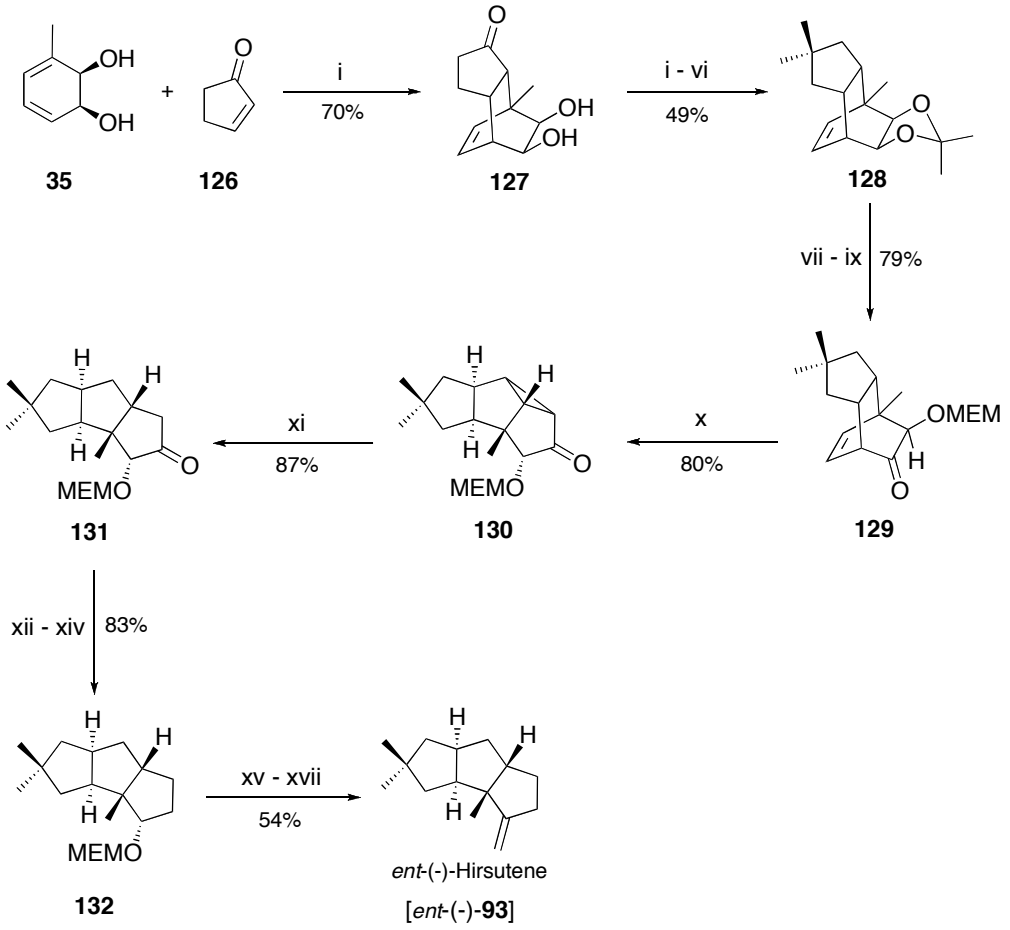
Scheme 2.5: *Reagents* (i) hν, acetone; (ii) tri-*n*-butyltin hydride, AIBN; (iii) NaH, allyl bromide; (iv) vinylmagnesium bromide, $CeCl_3$ (v) 2nd Gen. Grubbs' cat.; (vi) PCC.

2.2 Synthetic Strategy

The continued isolation of novel, highly functionalised and biologically active linear triquinane-type sesquiterpenoids has stimulated the ongoing development of new and more general strategies for assembly of the *cis:anti:cis* fused linear triquinane framework associated with this class of natural products. This Section describes work undertaken in the Banwell group directed towards the development of a general strategy for the enantioselective synthesis of a wide variety of linear triquinane type natural products, as well as their non-natural enantiomers.

2.2.1 The Banwell synthesis of *ent*-(-)-hirsutene

In 2002 Banwell *et al.* reported an enantioselective synthesis of the unnatural enantiomer of hirsutene [*ent*-(-)-**93**](Scheme 2.6).[73] To generate the linear triquinane core associated with this class of natural products in an enantioselective manner three key reactions were employed: (i) the enzymatic generation of optically pure starting material, (ii) a facially selective Diels-Alder cycloaddition and (iii) a photochemically-promoted oxa-di-π-methane rearrangement.



Scheme 2.6: *Reagents* (i) 19 kbar; (ii) $(MeO)_2CMe_2$, *p*-TsOH•H_2O; (iii) LiHMDS, MeI; (iv) $LiAlH_4$; (v) NaH, CS_2, MeI; (vi) tri-*n*-butyltin hydride, AIBN; (vii) AcOH; (viii) 4-acetamido-TEMPO, *p*-TsOH•H_2O; (ix) MEMCl, Hunig's base; (x) hν, acetophenone, acetone; (xi) tri-*n*-butyltin hydride, AIBN; (xii) $NaBH_4$; (xiii) NaH, CS_2, MeI; (xiv) tri-*n*-butyltin hydride, AIBN; (xv) PPTS; (xvi) PCC; (xvii) $Ph_3P{=}CH_2$.

Using enzymatically derived *c*-DHC[ß] **35** (see Chapter 1) as the enantiomerically pure starting material and drawing on previous work from within the group,[26] this diol was engaged in a high-pressure promoted Diels-Alder cycloaddition reaction with cyclopenten-2-one (**126**) to afford, as the major product of the reaction, the *syn*-adduct **127**. Protection of the diol moiety within this adduct as the corresponding acetonide then allowed for the installation of the *gem*-dimethyl group using LiHMDS and methyl iodide. Reduction of the carbonyl moiety and removal of the resultant hydroxy group using the Barton-McCombie deoxygenation protocol then gave compound **128**. The acetonide-protecting group was then cleaved under acid catalysis

ß This abbreviation for '*cis*-1,2-dihydrocatechol' is used throughout this Chapter.

and subsequent oxidation of the less hindered of the two hydroxy groups within the resulting diol was achieved using 4-acetamido-TEMPO. Owing to the instability of the resulting acyloin, the remaining hydroxyl group was protected as the MEM ether to afford compound **129**, the substrate for the key photochemical rearrangement.

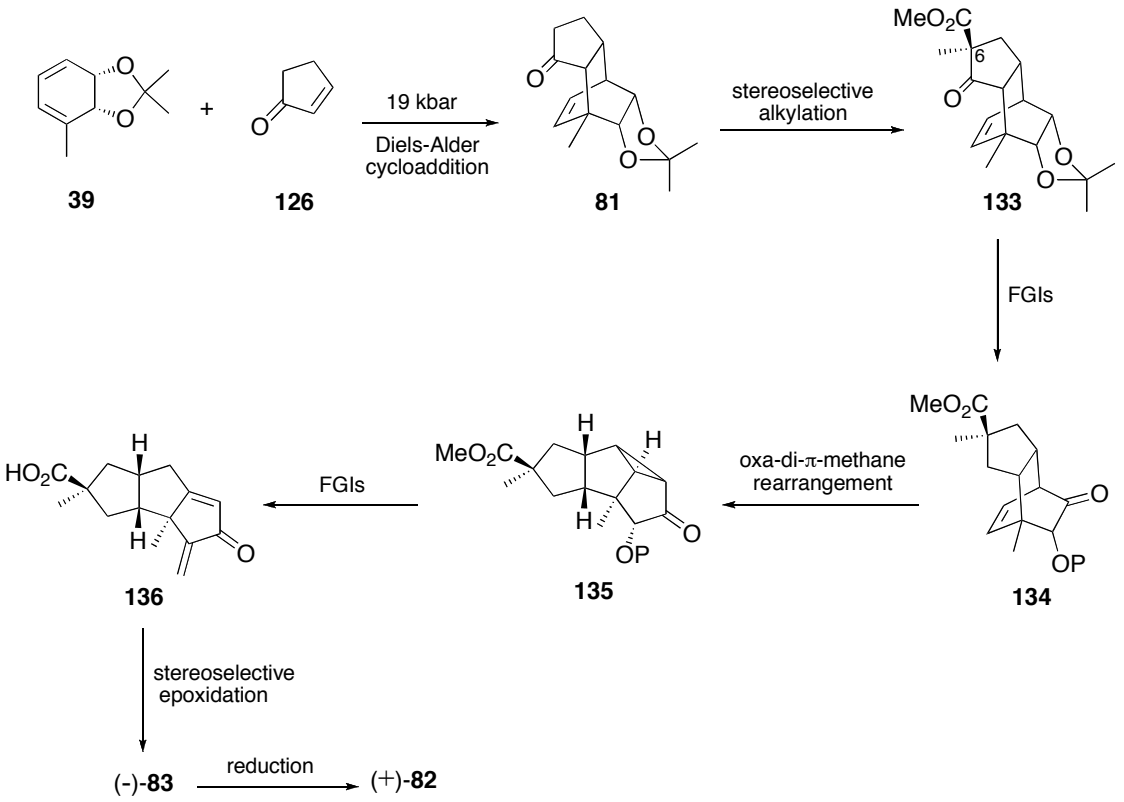
Compound **129** was irradiated under triplet-sensitised conditions to provide, *via* an oxa-di-π-methane rearrangement process, tetracycle **130** in 80% yield. Cleavage of the peripheral cyclopropane bond, which was formed during the photochemical rearrangement process, was achieved using tri-*n*-butyltin hydride and AIBN to give linear triquinane **131**. Removal of the carbonyl function, again using a hydride reduction/Barton-McCombie deoxygenation sequence, then furnished compound **132**, which was smoothly converted into *ent*-(-)-hirsutene [*ent*-(-)-**93**] in three steps using standard procedures.

2.2.2 Proposed synthetic route to (+)-hirsutic acid and (-)-complicatic acid

With a synthetic route to *ent*-(-)-hirsutene in hand, it was anticipated that this approach could be modified to enable synthesis of more highly functionalised members of the linear triquinane class of natural products. Moreover, by virtue of being able to control the facial selectivity of the Diels-Alder reaction, as described in Chapter 1, access to both enantiomeric series of these compounds should be possible. So, in light of their interesting biological profiles and in order to examine the scope of this chemistry that had been developed within the Banwell group, a synthetic route to (+)-hirsutic acid and (-)-complicatic acid was proposed (Scheme 2.7).

As in the synthesis of *ent*-(-)-hirsutene, it was envisaged that *c*-DHC **35** could be used as the enantiopure starting material. However, in order to obtain the correct absolute stereochemistry for the natural products, the Diels-Alder cycloaddition reaction must occur with the opposite facial selectivity; namely, *via anti*-addition of the dienophile to the diene. Based on previous studies in the group,[26] it was anticipated that this could be achieved by engaging the acetonide protected derivative of diol **35**, *viz.* compound **39,** in a high-pressure promoted Diels-Alder reaction with cyclopenten-2-one to afford cycloadduct **81**. It was also anticipated that the C6 quaternary centre (corresponding to C11 in the target molecule) would be able to be installed stereoselectively, to afford β-diketone **133,** using the protocols of Schuda and co-workers who had demonstrated in their syntheses of complicatic and hirsutic acids that alkylation occurs from only one face of rigid structures of this type.[64] Appropriate functional group interconversions should then give the substrate for the key photochemical rearrangement, namely β,γ-enone **134**.

It was envisioned that irradiation of β,γ-enone **134** under triplet sensitised conditions should result in an oxa-di-π-methane rearrangement to stereoselectively generate tetracycle **135**. Reductive cleavage of both the peripheral cyclopropane bond and the protected alcohol moiety followed by a series of standard functional group interconversions should then deliver dienone **136**, a key intermediate from which both complicatic acid and hirsutic acid have been synthesised by a number of groups.[61,70,71] The successful implementation of this strategy for the total synthesis of (-)-complicatic acid and (+)-hirsutic acid is described in the following Sections.



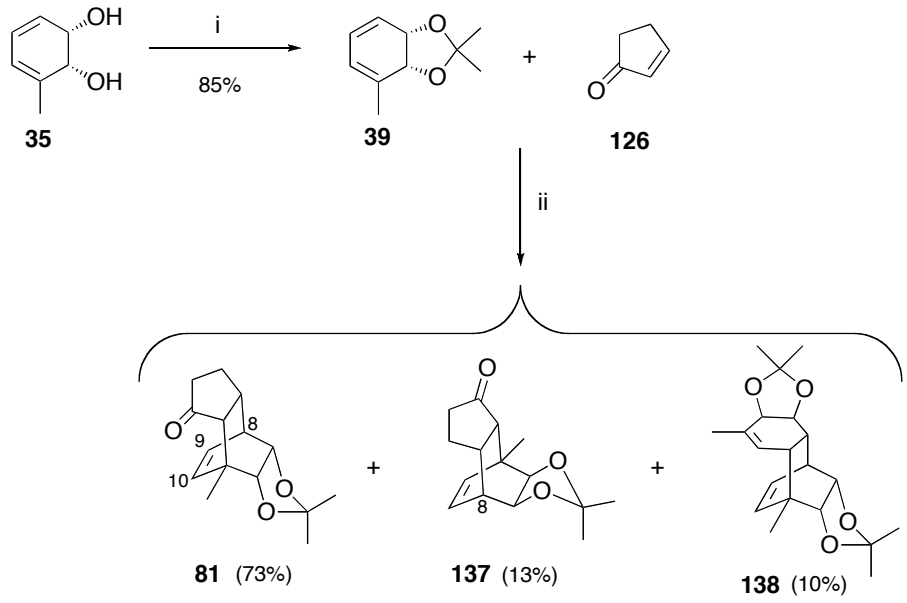
Scheme 2.7: *Proposed synthetic route to (-)-complicatic acid [(-)-**83**] and (+)-hirsutic acid [(+)-**82**].*

2.3 Total Syntheses of (+)-Hirsutic acid and (-)-Complicatic acid

2.3.1 The facially selective Diels-Alder cycloaddition reaction

As described in the previous Section, the establishment of syntheses of (-)-complicatic and (+)-hirsutic acids required effective control of the diastereofacial selectivity of the key Diels-Alder cycloaddition reaction. Based on studies of related Diels-Alder cycloaddition reactions performed by Stewart,[26] it was anticipated that the steric bulk imparted by an acetonide protecting group on the diol moiety should result in *anti*-addition of the dienophile to the diene to afford the *anti*-cycloadduct possessing the required stereochemistry.

To this end, toluene-derived *c*-DHC **35** was converted, under acid catalysis, into acetonide **39**, which was immediately reacted with cyclopenten-2-one (**126**) in a high-pressure promoted Diels-Alder cycloaddition reaction. This proceeded in a completely *endo*-selective manner to afford a chromatographically separable mixture of three products; the desired *anti*-adduct **81** (73%), its previously reported *syn*-isomer **137**[42] (13%) and Diels-Alder dimer **138** (10%) derived from the starting diene (Scheme 2.8).



Scheme 2.8: *Reagents and conditions* (i) $(MeO)_2CMe_2$, *p*-TsOH•H_2O, –10 to 18 °C, 1 h; (ii) cyclopenten-2-one (2.0 mole equiv.), CH_2Cl_2, 19 kbar, 18 °C, 24 h.

As is characteristic of Diels-Alder adducts of *c*-DHCs, the ^{1}H NMR spectrum of compound **81** (Figure 2.2) features a triplet at δ 6.12 (J = 8.3 Hz) and a doublet at δ 5.77 (J = 8.3 Hz), corresponding to C9-H and C10-H respectively, of the newly installed olefin. The multiplet at δ 2.92 was assigned to the bridgehead methine proton at C8. The analogous multiplet (C8-H) in the spectra of the corresponding *syn*-adduct[42] (**137**) is located at δ 3.09 and represents the key difference between the spectra of these isomers. The resonances assigned to the oxymethine protons of compound **81** appear at δ 4.25 and 3.81, further upfield than the equivalent signals in the starting material (**39**) and, as expected, a similar upfield shift is observed for the three singlets corresponding to the methyl groups. The presence of a molecular ion at *m/z* 248 in the electron impact (EI) mass spectrum, when considered in conjunction with the microanalytical data, confirmed the molecular formula as $C_{15}H_{20}O_3$. The stereochemistry of compound **81** was unequivocally established through single-crystal X-ray analyses of various derivatives (*ie* Figure 2.3, page 36), which show that cycloadduct **81** is formed through delivery, *via* an *endo*-transition state, of the dienophile to the face of the diene opposite the sterically demanding acetonide residue. The adjacent nature of the ketone carbonyl and methyl residues about the newly formed cyclohexene ring within adduct **81** derives from the operation of the *ortho*-rule.[22]

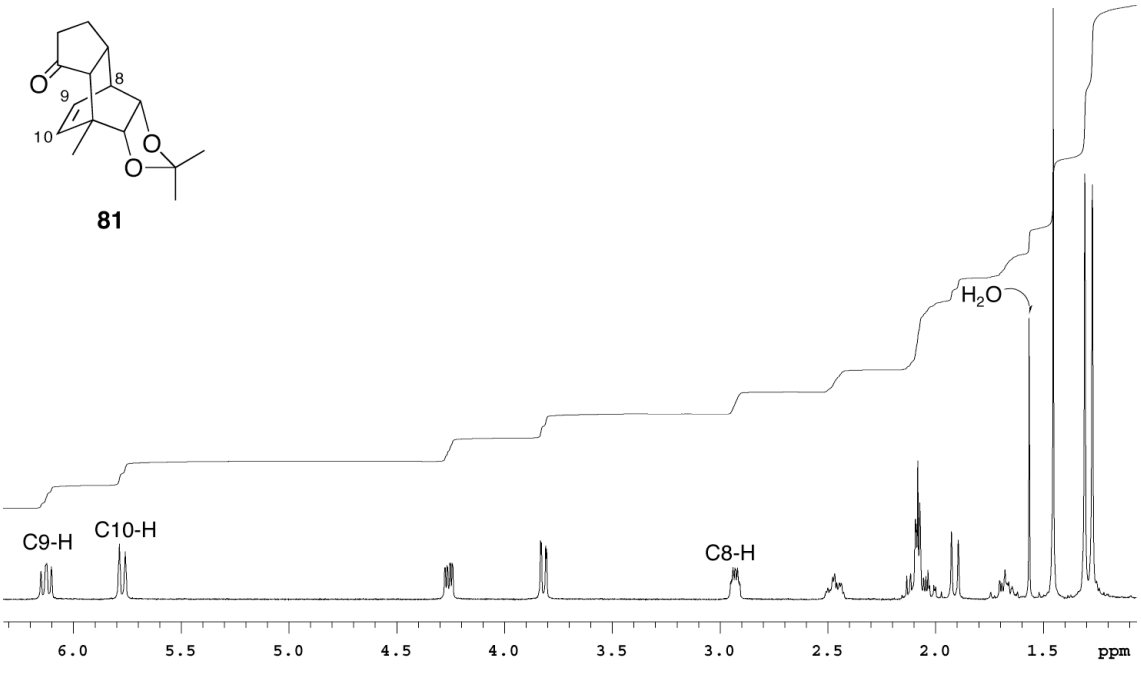
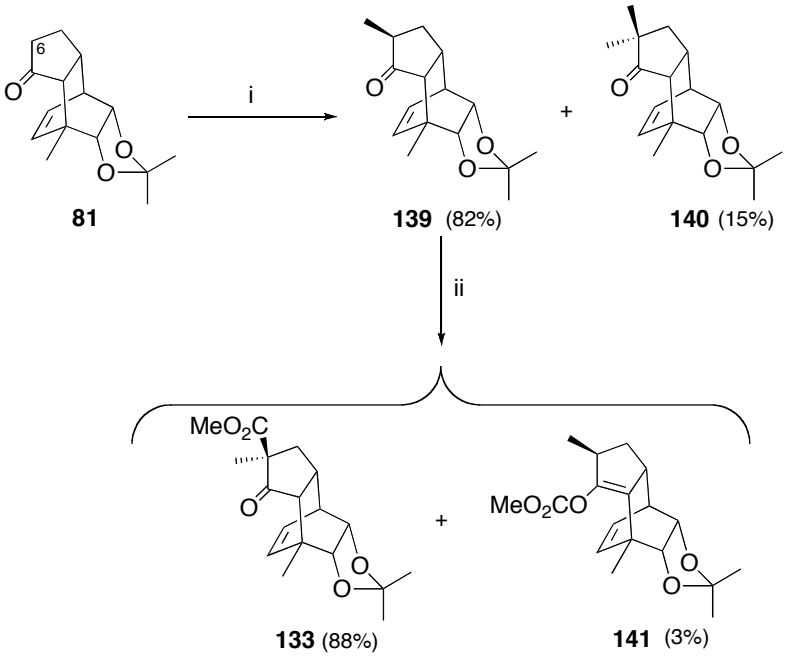


Figure 2.2: *300 MHz ^{1}H NMR spectrum of Diels-Alder adduct **81** (recorded in $CDCl_3$).*

2.3.2 Manipulation of the C ring[∝]

The next stage of the synthesis required stereoselective formation of a quaternary carbon centre at C6 of cycloadduct **81** (which corresponds to C11 of the target compounds). It was anticipated that because of the rigid nature of the cyclic framework, alkylation should occur from the *exo*-face of this compound.[64] Therefore, the methyl group should be introduced first, and the carbomethoxy group second to ensure the desired relative stereochemistry is established. To this end, the enolate derived from kinetic deprotonation of ketone **81** using LiHMDS was stereoselectively *C*-alkylated using methyl iodide and so affording a chromatographically separable mixture of methyl ketone **139** (82% at 92% conversion) and its *gem*-dimethylated equivalent **140** (15% at 92% conversion) (Scheme 2.9). Single-crystal X-ray analysis of methyl ketone **139** (Appendix 1) revealed that, as anticipated, addition had occurred from the *exo*-face and the carbon bearing the newly introduced methyl group possessed the *S*-configuration. Reaction of compound **139** with another aliquot of LiHMDS, and treatment of the ensuing enolate with methyl cyanoformate (Mander's reagent),[74] afforded β-keto-ester **133** in 88% yield, together with small amounts of enol carbonate **141** (3%). The structure of compound **141** was confirmed by single-crystal X-ray analysis (Appendix 2) and must arise *via O*-acylation of the ring-junction enolate derived from precursor **139**.



Scheme 2.9: *Reagents and conditions* (i) LiHMDS (1.1 mole equiv.), MeI (1.05 mole equiv.), THF, 0 to 18 °C, 4 h; (ii) LiHMDS (1.2 mole equiv.), $NCCO_2Me$ (2.0 mole equiv.), THF, 0 to 18 °C, 4 h.

∝ See Figure 2.1, page 21 for the labelling of the three five-membered rings of the triquinane framework.

The most notable feature within the ^{1}H NMR spectrum of compound **133** is the presence of two new singlets at δ 3.66 and 1.17, each of which integrates for three protons. They were assigned, respectively, to the methoxy moiety of the ester and the methyl group attached to the newly formed quaternary centre. The appearance of resonances at δ 173.0 and 51.9 in the ^{13}C NMR spectrum of this same material are considered diagnostic for the presence of a methyl ester, while the signal at δ 58.4 is characteristic of a β-keto-ester and was determined, by APT (attached proton test) ^{13}C NMR spectroscopy, to be due to a quaternary carbon. Carbonyl stretching bands were observed in the IR spectrum, at 1753 and 1728 cm^{-1}, as would be expected for keto-ester **133**. The relative stereochemistry was confirmed by single-crystal X-ray analysis (Figure 2.3, Appendix 3).

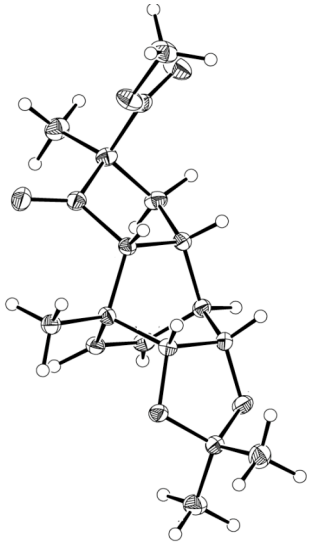


Figure 2.3: *Displacement Ellipsoid Plot (30%[◈]) derived from single-crystal X-ray analysis of β-keto-ester **133**.*[☾]

In addition to the linear triquinoid-type natural products described above, there are a number of related compounds, such as (-)-phellodonic acid [(-)-**142**], that possess the same functionalities at C11 although the stereochemistry at this centre now is *S* rather than *R*. (Figure 2.4).

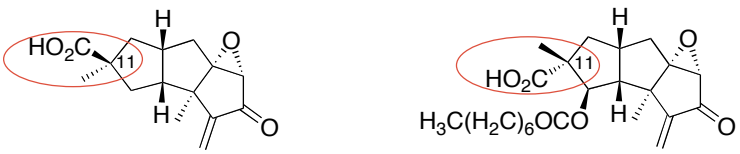
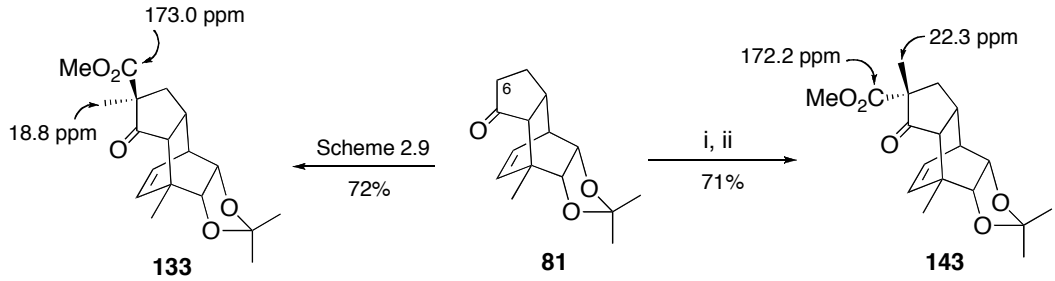


Figure 2.4: *(-)-Complicatic acid and (-)-phellodonic acid showing the opposite configuration at C11.*

◈ The anisotropic displacement ellipsoids show 30% probability levels.

☾ The numbers of the crystal structures within this thesis have been omitted for clarity. Please see appropriate appendices for numbered structures and full X-ray structure reports.

In light of this, and in order to confirm the rational behind this synthetic method, the C6 epimer of compound **133** was synthesised by reversing the order of the methylation and acylation steps (Scheme 2.10). Thus, the kinetic enolate of compound **81** was generated as previously described and treated with methyl cyanoformate. Because the resultant 1,3-dicarbonyl compound was obtained as a mixture of readily interconverting tautomers, full characterisation of this product was not possible. Therefore, the C6 configuration was not determined at this stage. Nevertheless, when this tautomeric mixture was treated with sodium hydride followed by methyl iodide the β-keto-ester **143** was obtained. This possesses a C6 configuration opposite to that of the previously prepared β-keto-ester **133**.



Scheme 2.10: *Reagents and conditions* (i) LiHMDS (1.5 mole equiv.), $NCCO_2Me$ (1.1 mole equiv.), THF, -78 to 18 °C, 14 h; (ii) NaH (2.0 mole equiv.), MeI (5.0 mole equiv.), THF, 0 to 18 °C, 2 h.

Although the spectral data obtained on compound **143** were very similar to those of congener **133**, comparison of the ^{13}C NMR spectra provided convincing evidence that the opposite stereochemistry had been established at C6.[θ] Thus, in the spectrum of keto-ester **133** the signal attributed to the *endo*-oriented C6-methyl group is observed at δ 18.8 while for epimer **143** (Figure 2.5) the equivalent signal, for the *exo*-oriented C6-methyl group, is observed downfield, at δ 22.3. Similarly, the signal attributed to the carbonyl-carbon of the methyl ester moiety is observed further downfield when it is in the *exo*-position (compound **133**, δ 173.0) as compared to the when it is in the *endo*-position (compound **143**, δ 172.2). The other sixteen resonances appear at very similar chemical shifts in both epimers.

θ The stereochemistry of β-keto-ester **143** was later confirmed by single-crystal X-ray analysis of a derivative of this compound, and shown to be as illustrated.[28]

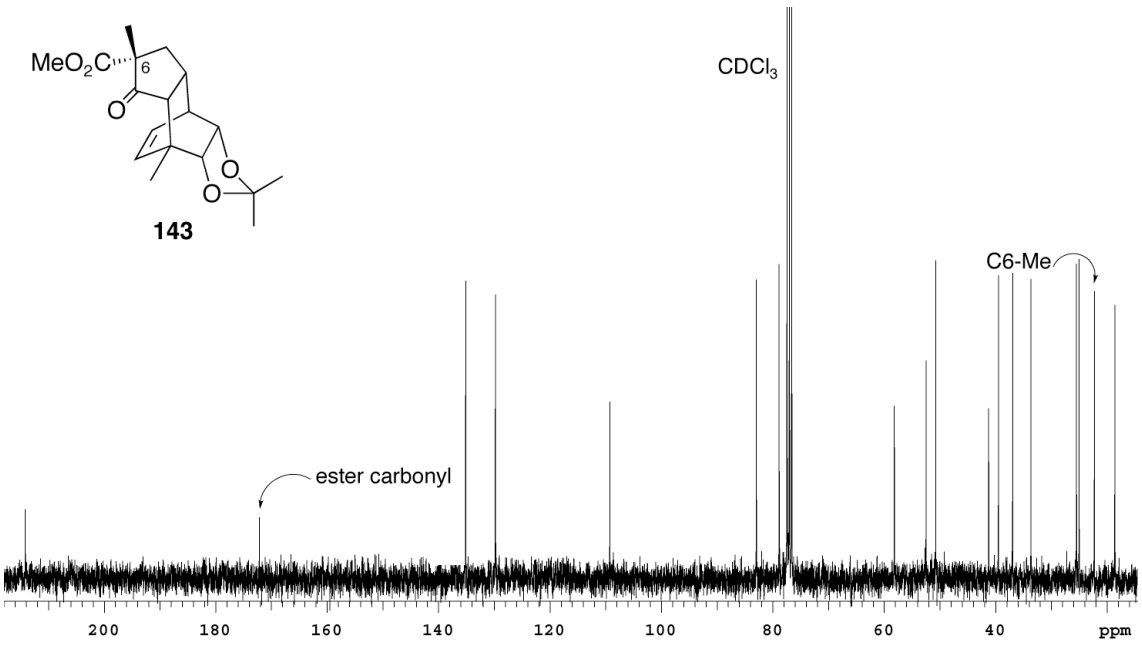
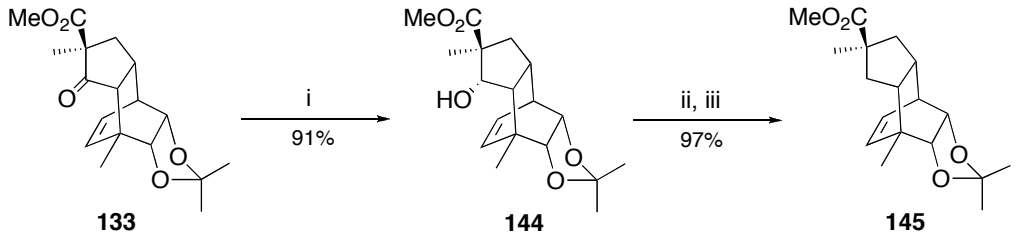


Figure 2.5: *300 MHz ^{13}C NMR spectrum of β-keto-ester **143** (recorded in $CDCl_3$).*

The ketone carbonyl group derived from the dienophile had to this point been an essential element in this synthesis owing to the activating and directing effects it exerted in the Diels-Alder cycloaddition reaction and because it provided the means by which to install the adjacent C6 methyl and carbomethoxy groups. However, at this point in the synthesis it was no longer required so methods for its removal were explored. Approaches involving direct deoxygenation such as the Wolff-Kishner and Clemmensen protocols require strongly basic or acidic conditions and could not, therefore, be used due to the presence of the acetonide and β-keto-ester moieties. A modified Clemmensen reduction[75] using zinc and gaseous hydrochloric acid in THF or Et_2O was investigated but without success. Attempts at forming the tosylhydrazone or thioketal were similarly unsuccessful. Accordingly, the hydride-reduction/Barton-McCombie deoxygenation[76] sequence used by Harfoot in his synthesis of *ent*-(-)-hirsutene was explored (Scheme 2.11).[42] To such ends, the ketone carbonyl of β-keto-ester **133** was reduced. Initial attempts involved the use of sodium borohydride in MeOH which, by itself, yielded an epimeric mixture of alcohols in a disappointing 65% yield. However, when cerium trichloride was added to the reaction mixture (Luche conditions)[77] the reduction was found to proceed in a completely stereoselective manner and to afford alcohol **144** in a much improved yield (91%). All the spectral data derived from compound **144** were consistent with the formation of the desired product. The IR spectrum proved particularly diagnostic and was consequently used to monitor the reaction as the product and starting material were found to co-migrate under thin layer chromatographic (tlc) conditions. A new IR absorbance at 3541 cm^{-1}, together with the disappearance of the stretching band attributable to the ketone carbonyl (1753 cm^{-1}) indicated that the desired reduction of the ketone had occurred. The orientation of

the newly introduced hydroxy group of alcohol **144** was determined by single-crystal X-ray analysis (Appendix 4). This stereochemistry is thought to arise from chelation control of the reduction by the added cerium.[ω]

Alcohol **144** was converted into the corresponding *S*-methyl xanthate ester by using NaHMDS to form the corresponding sodium alkoxide and treating this with carbon disulfide and methyl iodide. Radical cleavage of the ensuing ester using tri-*n*-butyltin hydride and AIBN in refluxing toluene proceeded smoothly to give the deoxygenated compound **145** in 97% yield (from alcohol **144**) over the two steps involved (Scheme 2.11).



Scheme 2.11: *Reagents and conditions* (i) $CeCl_3 \cdot 7H_2O$ (4.0 mole equiv.), $NaBH_4$ (1.0 mole equiv.), MeOH, 0 to 18 °C, 5 h; (ii) NaHMDS (2.0 mole equiv.), CS_2 (2.0 mole equiv.), MeI (2.1 mole equiv.), 0 to 18 °C, 6 h; (iii) tri-*n*-butyltin hydride (4.0 mole equiv.), AIBN, toluene, *ca*. 110 °C, 5 h.

2.3.3 Deprotection of the acetonide and unexpected formation of a hemiorthoester

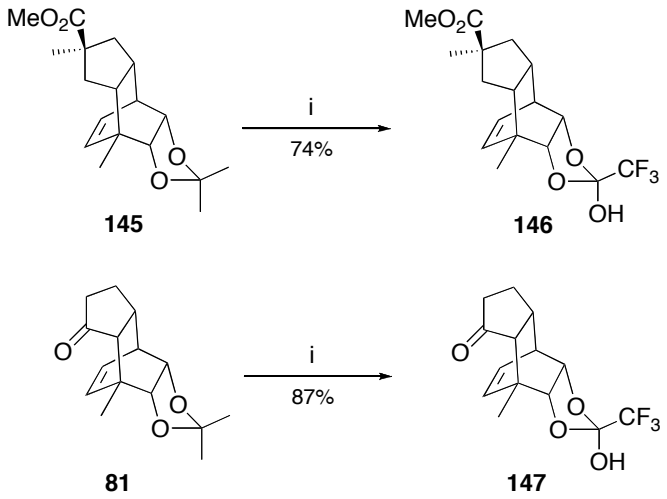
With compound **145** in hand, attention turned towards the elaboration of this material into the β,γ-unsaturated ketone required for the key photochemical rearrangement. Following the proposed synthetic strategy, the first step in the relevant sequence involves acetonide deprotection.

Cleavage of the acetonide residue within compound **145** proved somewhat problematic. While such moieties are normally quite susceptible to acid hydrolysis, this process was difficult to accomplish with substrate **145** when conventional conditions were used. This is presumably due to the rigid nature of the bicyclo[2.2.2]octene framework to which the acetonide unit is

ω When the C6-epimeric keto-ester **143** was subjected to these reduction conditions the epimeric alcohol was produced. This indicates that unlike the facial selectivity of the alkylation steps, which is controlled by the rigid framework, the facial selectivity of the reduction is controlled by the C6 stereochemistry.[78]

annulated. Attempts to obtain the desired diol involved the use of conditions such as 2 M aqueous HCl,[79] aqueous HCl in THF[80] (various concentrations), acetic acid in water,[42] mercaptoethanol with a Lewis acid (eg boron trifluoride diethyl etherate[81]) and iodine in MeOH (1% *w/v*)[82]. Little success was observed under such conditions.

Hydrolysis of the acetonide residue of compound **145** was subsequently attempted with trifluoroacetic acid (TFA).[83] Although small amounts of the expected diol were obtained, at 18 ºC, using TFA in the presence of small quantities of water, the hydrolysis was slow and inefficient. Unexpectedly, after 72 h the major product was not a diol but a compound that was less polar than the starting material. The same type of result was observed when acetonide **81** was subjected to these reaction conditions (Scheme 2.12). Analysis of the spectroscopic data led to the identification of these products as hemiorthoesters **146** and **147**. Each of these compounds was accompanied by small amounts (<10%) of the corresponding acetonides and diols.



Scheme 2.12: *Reagents and conditions* (i) TFA, H_2O, 18 ºC, 3 days.

Compounds **146** and **147** were both obtained as single diasteriomers and each was subject to various spectroscopic analyses, although the unstable nature of compound **146** made characterisation problematic. The EI mass spectrum of hemiorthoester **147** displayed a molecular ion at *m/z* 304 and accurate mass measurement on this species established it possessed the molecular formula $C_{14}H_{15}F_3O_4$. The infrared spectrum revealed a carbonyl stretching band at 1714 cm^{-1} that is attributed to the ketone moiety. Since trifluoroacetate-type carbonyl stretching bands appear at *ca.* 1780–1790 cm^{-1}, this suggests that compound **147** does not exist, to any significant extent, in its open-chain/mono-trifluoroacetate ester form. The 300 MHz ^1H NMR spectrum of hemiorthoester **147** contained oxymethine proton resonances in

similar positions to those arising from the equivalent protons in precursor **81**. This suggests a 1,3-dioxolane ring is still present in compound **147**. The 75 MHz ^{13}C NMR spectrum displays twelve of the expected fourteen resonances, with those resulting from the hemiorthoester and CF_3-group carbons not being observed. The spectral features just described were also observed for congener **146**. Single-crystal X-ray analysis (Figure 2.6, Appendix 5) allowed for unambiguous assignment of the illustrated structure to compound **147** and revealed the cyclic hemiorthoester moiety has the CF_3-group in the *exo*-orientation.

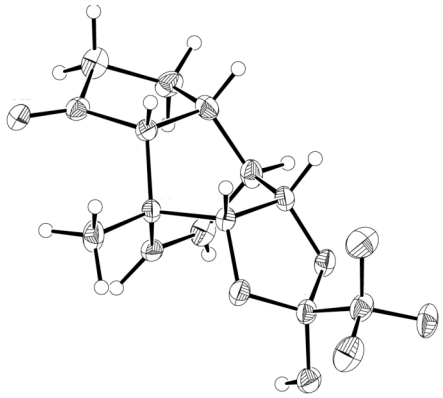
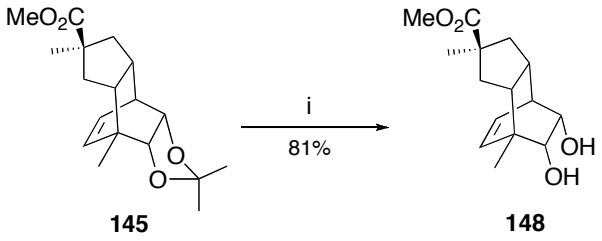


Figure 2.6: *Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of hemiorthoester **147**.*

After thorough investigation, the optimal conditions for the generation of diol **149** from acetonide **145** proved to involve heating the latter material at 110 °C in MeOH/H_2O for 5 days in the presence of freshly activated DOWEX-50 resin (Scheme 2.13).[84,85] In this manner the target diol **149** was obtained in 81% yield.



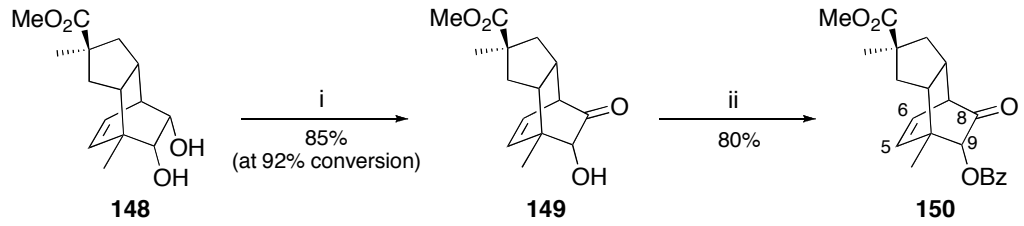
145 **148**

Scheme 2.13: *Reagents and conditions* (i) DOWEX-50 resin (acidic form), MeOH/H_2O (5:1), 110 °C, 5 days.

2.3.4 Formation of the β,γ-unsaturated ketone substrate required for the photochemically promoted oxa-di-π-methane rearrangement

With diol **149** in hand, the next step required oxidation of one of the alcohol moieties to obtain the β,γ-enone motif necessary for the oxa-di-π-methane rearrangement. Oxidation of the less hindered of the two hydroxyl groups was achieved using the sterically demanding oxo-ammonium salt derived from *p*-TsOH•H_2O-promoted disproportionation of 4-acetamido-TEMPO.[86] This afforded acyloin **149** in 85% yield (at 92% conversion) (Scheme 2.14).

In principle, acyloin **149** could have been subjected to the photochemical rearrangement. However, it had been observed previously that dimerization of related acyloins occurs readily and, as a consequence, the photorearrangement of such compounds can be very inefficient.[87] Such difficulties can be completely avoided by protection of the hydroxyl group. It is important that the protecting group chosen is photochemically inert, and not overly bulky because it might otherwise inhibit the rearrangement process. It was also envisaged that the *O*-protected hydroxyl group could be removed *via* a reductive elimination process in an effort to simultaneously remove both the cyclopropane and C1-hydroxyl moiety, thereby saving at least one step in the reaction sequence. A search of the literature revealed the benzoyl protecting group should be suitable for both purposes.[88,89] Accordingly, acyloin **149** was converted, under standard conditions and in 80% yield, into the corresponding benzoate **150** (Scheme 2.14) and this material became the substrate for the photochemical studies outlined in the following Section.



Scheme 2.14: *Reagents and conditions* (i) 4-acetamido-TEMPO (2.2 mole equiv.), *p*-TsOH•H_2O (2.2 mole equiv.), CH_2Cl_2, 0 to 18 °C, 22 h; (ii) benzoyl chloride (3.5 mole equiv.), DMAP (3.5 mole equiv.), Et_3N (4.7 mole equiv.), CH_2Cl_2, 0 to 18 °C, 17 h.

The ^{1}H NMR spectrum of benzoate **150** (Figure 2.7) features signals in the aromatic region along with a single at δ 5.09 that is assigned to the oxymethine proton of the newly protected *O*-hydroxy moiety. The ^{13}C NMR spectrum (Figure 2.8) features resonances associated with the

β,γ-unsaturated ketone framework at δ 139.4, 127.0 and 205.3. These are assigned to C5, C6 and C8, respectively. A signal at δ 74.0 is attributed to the C9 oxymethine carbon. There is a complete absence of absorbances attributed to free hydroxyl groups in the IR spectrum, indicating protection of this moiety has occurred. Finally, single-crystal X-ray analysis (Appendix 6) of compound **150** confirmed that no epimerisation of the hydroxyl group had occurred under the reaction conditions used for this conversion.

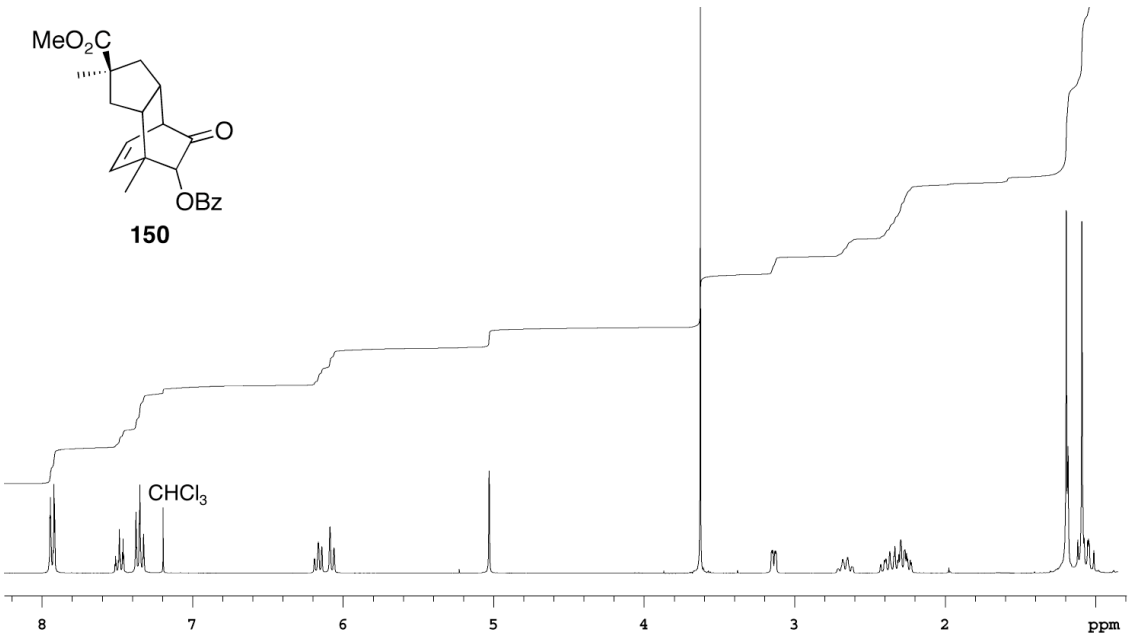


Figure 2.7: *300 MHz ^{1}H NMR spectrum of benzoate **150** (recorded in $CDCl_3$).*

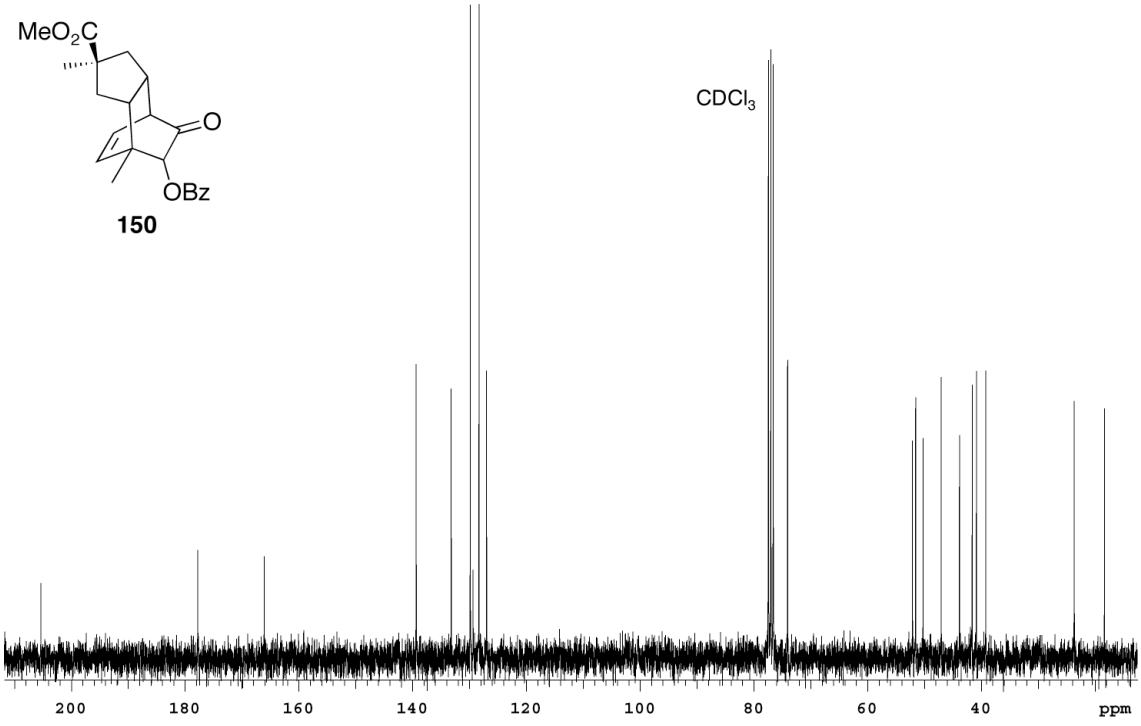
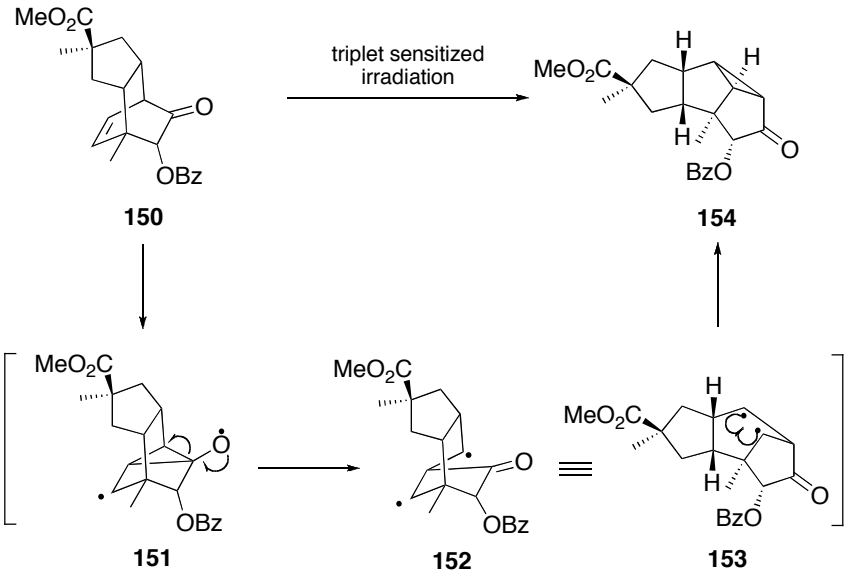


Figure 2.8: *300 MHz ^{13}C NMR spectrum of benzoate **150** (recorded in $CDCl_3$).*

2.3.5 The oxa-di-π-methane (ODPM) rearrangement [90,91]

Photochemical rearrangements of β,γ-unsaturated ketones incorporated within a rigid framework, such as seen in compound **150**, can occur *via* two distinct pathways, resulting in either a 1,2- or a 1,3-acyl shift.[92] The title rearrangement is a triplet-mediated photochemical process resulting in a 1,2-acyl shift, with concurrent formation of a cyclopropyl ketone. Demuth and co-workers have described this reaction pathway as involving a series of biradical intermediates (Scheme 2.15). Evidence for this stepwise pathway has been obtained in in three separate studies.[93]



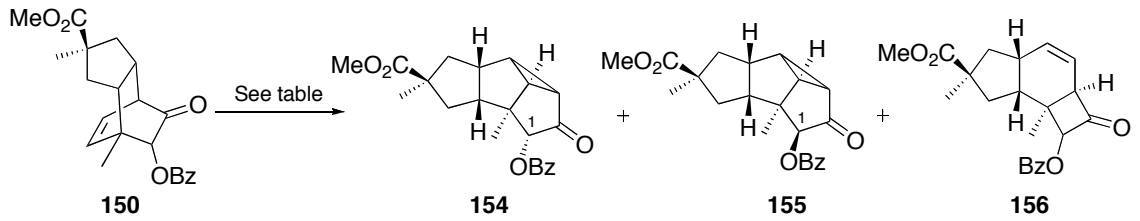
Scheme 2.15*: Pathway for the oxa-di-π-methane rearrangement proposed by Demuth* et al.[93]

It was recognised by Singh *et al.*, that as the relative stereochemistry at the ring junctions of the rearranged product are governed by the relative stereochemistry of the β,γ-unsaturated ketone, the desired *cis:anti:cis* triquinane framework can be accessed if the third ring is annulated onto the bicyclic framework in an *endo*-fashion.[94] Furthermore, the ODPM rearrangement is expected, on mechanistic grounds, to occur with retention of configuration at all centres. Accordingly, tetracycle **154** is the expected product of the oxa-di-π-methane rearrangement of compound **150**.

In order to bring about the desired rearrangement, compound **150** was irradiated under triplet sensitised reaction conditions. To promote triplet excitation, the reaction was conducted in acetone with added acetophenone as both these ketones are triplet sensitisers. Additionally, the reaction mixture was jacketed by a UV filter solution containing NaBr (750 g/L) and $Pb(NO_3)_2$

(8 g/L) to ensure that the wavelength of the transmitted light is greater than 340 nm.[95] As revealed in Table 2.1, depending upon the precise conditions, including reaction time, substrate concentration and the number of equivalents of acetophenone employed, varying proportions (and yields) of three photoproducts, compounds **154**, **155** and **156**, were obtained.

Table 2.1: *The photochemically promoted rearrangement of compound **150***

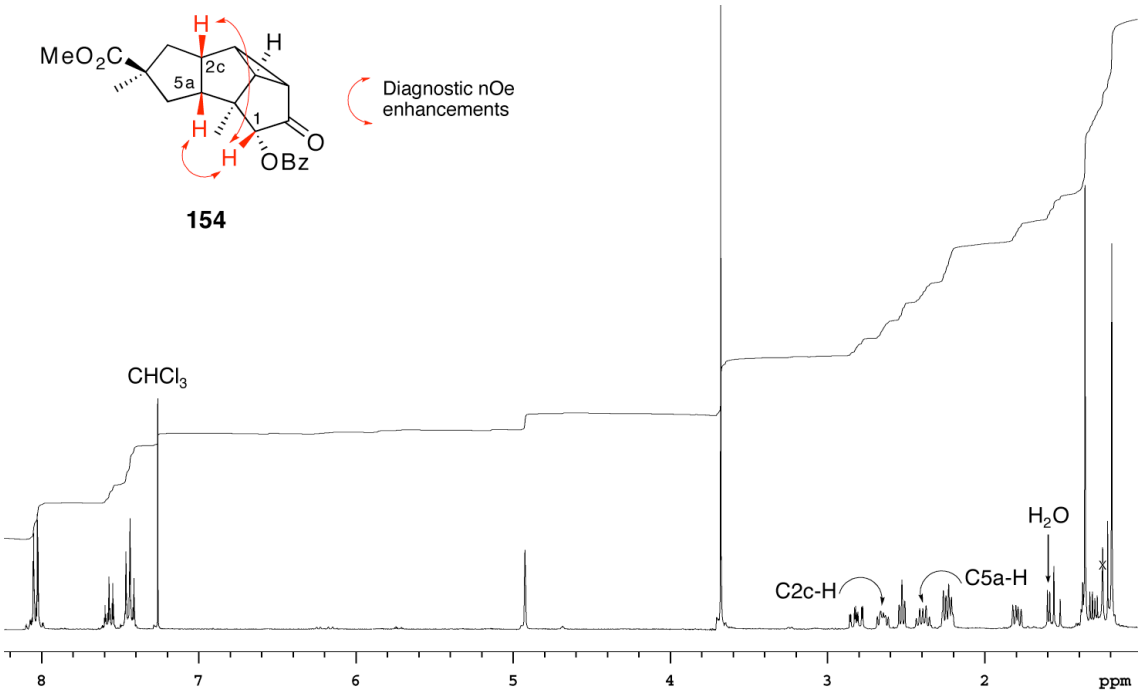


150 **154** **155** **156**

Entry	concentration	acetophenone (equiv.)	time	**154**	**155**	**156**	conversion
1	0.17 M	0.2	24 h	1	1	2.3	62%
2	0.17 M	2.5	36 h	1	1	1.9	64%
3	0.03 M	2.5	36 h	1.7	6.7	1	93%
4	0.02 M	2.5	80 h	1	9.1	traces	100%
5	0.01 M	2.5	24 h	1	7.6	1.5	95%

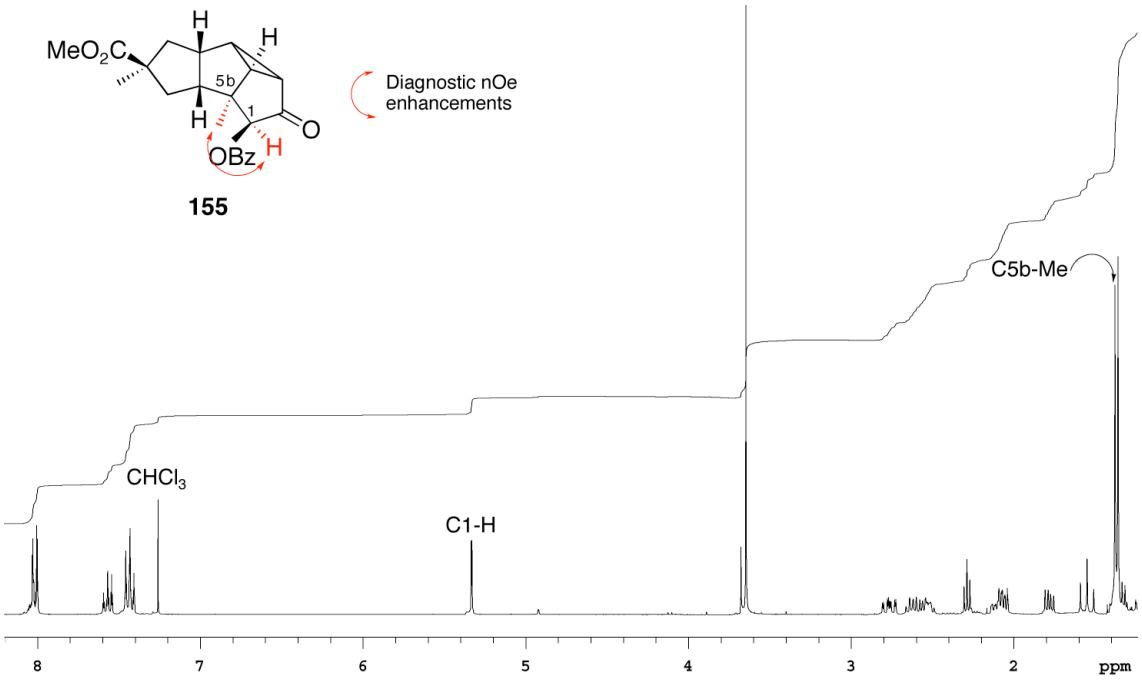
Tetracycles **154** and **155** were identified as products of the desired oxa-di-π-methane rearrangement of β,γ-enone **150**. Accurate mass measurements on the molecular ions observed at *m/z* 368 in the EI mass spectrum of each of these compounds established the molecular formula, $C_{22}H_{24}O_5$, indicating that they are isomeric with the starting material, as expected for a rearrangement process. The absence of olefinic resonances in the ^{1}H NMR spectra also provided evidence that the desired rearrangement had occurred in both instances. Although the ^{1}H NMR spectra of photoproducts **154** and **155** (Figure 2.9 and 2.10 respectively) are similar, there is a notable difference in the position of the peaks attributed to the C1-oxymethine proton, at δ 4.92 and 5.34 respectively. On this basis it was proposed that it is at this C1 centre that the two compounds differ. Accordingly, assignment of the stereochemistry of each compound was carried out using nOe techniques. Thus, a strong nOe correlation was observed between the C1-H and C5a-H and a weak correlation between C1-H and C2c-H in compound **154** (Figure 2.9). In contrast, for compound **155** there was only a weak correlation observed between C1-H and the C5b-methyl group. This indicated that while tetracycle **154** was the expected product, in

which the rearrangement had occurred with retention of stereochemistry, tetracycle **155** had undergone inversion at C1.



154

Figure 2.9: *300 MHz ^{1}H NMR spectrum of photoproduct **154** (recorded in $CDCl_3$).*



155

Figure 2.10*: 300 MHz ^{1}H NMR spectrum of photoproduct **155** (recorded in $CDCl_3$).*

Cyclobutanone **156** (Table 2.1) was presumed to arise from the undesired 1,3-acyl migration process, a recognized result of direct singlet irradiation of substrates such as β,γ-enone **150**.[43]

The mechanism in this case involves initial α-cleavage of the ketone, thereby creating an acyl/allyl biradical. Recombination from the alternative allylic position forms the 1,3-acyl shift product.[90] The presence of a cyclobutanone moiety was established by examination of the IR spectrum, which exhibits a prominent ketone carbonyl absorption at 1790 cm^{-1} (*cf*. 1740 cm^{-1} in tetracycles **154** and **155**). The ^{13}C NMR spectrum features a resonance at δ 200.3, which is in a significantly different position to the equivalent resonances for photoproducts **154** and **155** (δ 209.7 and 206.1 respectively). Once again, the EI mass spectrum features a molecular ion at *m/z* 368, for which an accurate mass was obtained, thereby indicating that compound **156** is isomeric with starting material **150**. The ^{1}H NMR spectrum features a pair of signals, at δ 5.75 and 5.63, arising from the two olefinic protons. Whilst compound **156** was isolated as a single diastereomer, the configuration at the benzoyloxy-bearing carbon was not determined.

The various experiments shown in Table 2.1 revealed that the best proportions of the desired compounds **154** and **155** were achieved using 2.5 equivalents of acetophenone. Lowering the amount of this sensitizer to 0.2 equivalents resulted in a predominance of the undesired cyclobutanone **156**. The concentration of the substrate was also important, with more dilute solutions producing more satisfactory outcomes. Under the optimal conditions, namely irradiation of an 0.02 M solution of compound **150** in acetone with 2.5 equivalents of acetophenone maintained at 5 to 10 °C for 80 h, full conversion of the substrate could be achieved and only small amounts of cyclobutanone **156** were formed (Scheme 2.16).

With conditions in hand that reduced the production of undesired side products attention was turned to investigating, in detail, the modes of the formation of the two ODPM products **154** and **155**. The ratio of photoproducts **154** and **155** was found to be highly dependant upon the reaction time employed. As shown in Figure 2.11, the former compound is produced first and then converted into the latter.

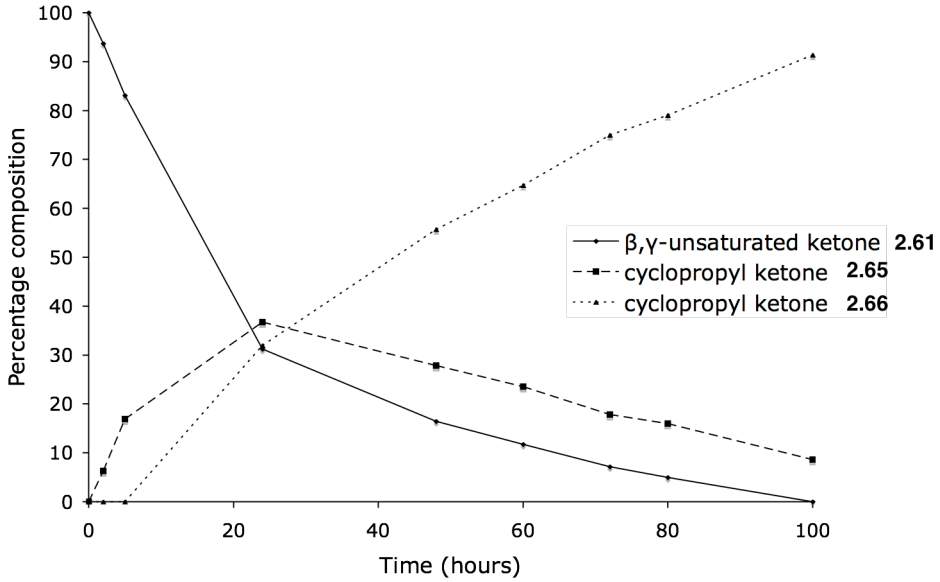
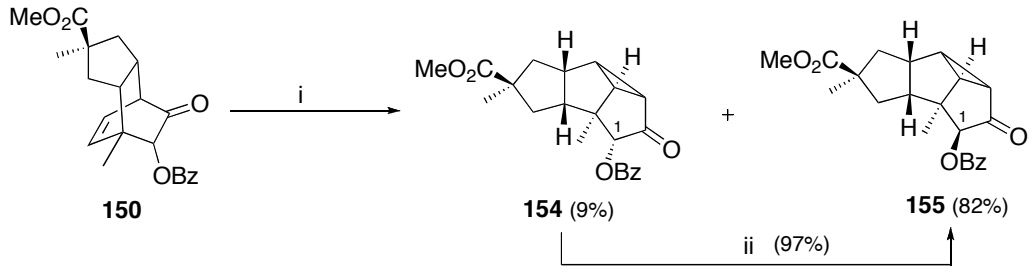


Figure 2.11: *Graph of percentage composition vs. time (hours) for the oxa-di-π-methane rearrangement reaction of β,γ- unsaturated ketone* ***150****.*

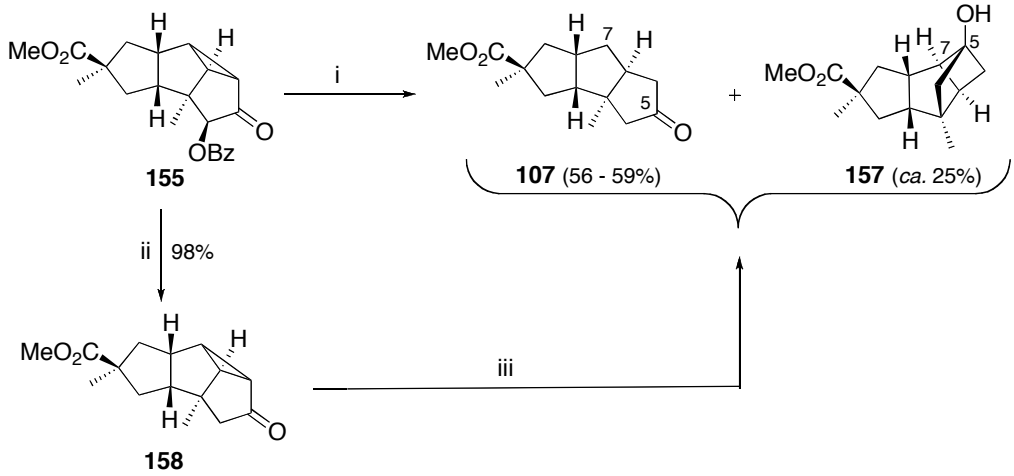
In a control experiment, compound **154** was subjected to the original irradiation conditions and was converted, over a period of 36 h and in 97% yield, into epimer **155** (Scheme 2.16). This presumably involves a photoenolization process[96] and the driving force for this is most probably the relief of steric congestion between the abutting angular methyl and benzoyloxy groups in the primary photoproduct. As the removal of the C1-benzyloxy group was the planned next step, the stereochemistry at this centre is not important, so, and in most cases, the reaction was run until the starting material had been consumed, thus generating a mixture of the major two photoproducts.



Scheme 2.16: *Reagents and conditions* (i) hν (125 W Philips HPL-N lamp), UV filter [NaBr 759 g/L, $Pb(NO_3)_2$ 8 g/L], acetophenone (2.5 mole equiv.), acetone, 5 to 10 °C, 80 h (ii) as in (i), 36 h.

2.3.6 Reductive cleavage of the *O*-benzyloxy group and the cyclopropane ring

As noted earlier, it was anticipated that compounds **154** and **155** could both be elaborated to the target natural products as the next stage involved reductive cleavage of the C1-benzyloxy group. Samarium (II) iodide (SmI_2) was used for this purpose in the expectation that this reagent should effect reductive cleavage of both the C1-benzoyloxy group[88] and the carbonyl-conjugated cyclopropane ring[97] and so forming the required linear triquinane framework in a single step. To this end, the major photoproduct, **155**, was treated with four mole equivalents of SmI_2 in THF/MeOH between -78 °C and 18 °C for a total of 3 h. However, the desired product **107** (56%) was accompanied by significant quantities of cyclobutanol **157** (25%) (Scheme 2.17). In order to understand the formation of this by-product, the two separate transformations, cleavage of the *O*-benzyloxy moiety and cleavage of the cyclopropane, were carried out independently (Scheme 2.17). Thus, it was determined that when tetracycle **155** was treated with two equivalents of SmI_2 at -78 °C only cleavage of the benzoyloxy moiety occurred, producing compound **158** in high yield. When this material was resubjected to reaction with SmI_2 at -78 °C, no reaction occurred. However, on warming to room temperature formation of both tricycle **107** (59%) and cyclobutanol **157** (25%) was observed.



Scheme 2.17: *Reagents and conditions* (i) SmI_2 (4.0 mole equiv.), THF/MeOH, −78 to 18 °C, 3 h; (ii) SmI_2 (2.2 mole equiv.), THF/MeOH, −78 °C, 10 min; (iii) SmI_2 (2.2 mole equiv.), THF/MeOH, 18 °C, 2 h.

The formation of compound **157,** although unexpected, can be easily explained. It presumably involves initial reductive removal of the C1-benzoyloxy group, followed by cyclopropane ring cleavage to deliver a compound bearing a radical at C7. Rather than being quenched by an external proton source, the C7 radical combines in an intramolecular fashion with the ketyl

radical at C5 to afford the observed tertiary alcohol. Hoffmann and co-workers have observed similar conversions by employing SmI_2 for the pinacolic coupling of 1,4-diketones so forming cyclobutene-1,2-diols embedded within polycyclic frameworks.[98] The structure of by-product **157** was confirmed by single-crystal X-ray analysis of the *p*-nitrobenzoyl derivative (obtained in 75% yield from **157**) (Figure 2.12, Appendix 7).

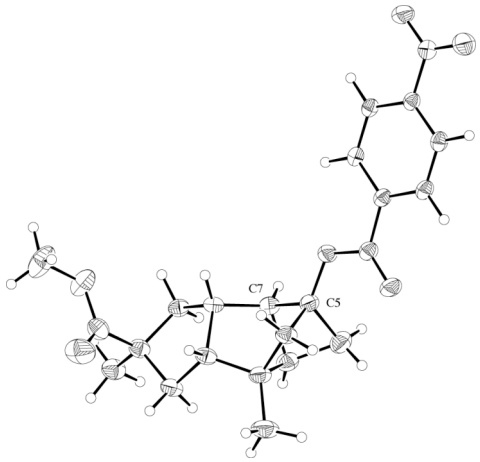
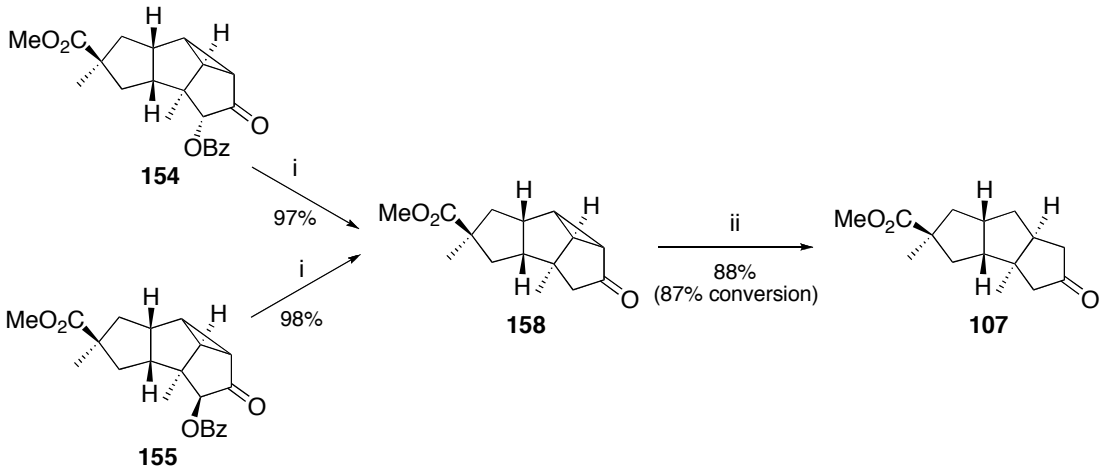


Figure 2.12: *Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of* p-*nitrobenzoyl derivative of alcohol **157**.*

After this discovery, an alternate route to compound **107** was sought. Using the protocol described above, compound **155** was debenzoylated, in 98% yield, by brief exposure to two equivalents of SmI_2 at -78 ºC to afford compound **158**. Analogous treatment of the C1-epimer, **154**, produced the same outcome, namely generation of the desired product, **158**, in 97% yield (Scheme 2.18).



Scheme 2.18: *Reagents and conditions* (i) SmI_2 (2.2 mole equiv.), THF/MeOH, −78 °C, 10 min; (ii) tri-*n*-butyltin hydride (6.0 mole equiv.), AIBN (trace), benzene, reflux, 1.5 h.

Following procedures established by Singh *et al.*,[68] compound **158** was then treated with six mole equivalents of tri-*n*-butyltin hydride and AIBN in refluxing benzene to cleave the cyclopropane ring and so form triquinane **107**, which was obtained as the sole reaction product in 88% yield (at 87% conversion).

Compound **107** is an advanced intermediate associated with the synthesis of (+)-hirsutic acid and (-)-complicatic acid reported by Greene *et al*.[71] Accordingly, its acquisition constitutes a formal total synthesis of both these natural products. Although the ^{1}H and ^{13}C NMR (Figure 2.13) spectra of compound **107** could not be directly compared to the spectral data reported in the literature (due to the use of different solvents and the fact that Greene *et al.* reported only limited data) these are entirely consistent with the proposed structure and could be fully assigned using a variety of NMR connectivity experiments. Furthermore, all other spectral data collected were consistent with the equivalent data reported for Greene's compound. In particular, the optical rotation obtained for compound **107** ($[\alpha]_D$ = -121) is in full agreement with the value reported by Greene and co-workers ($[\alpha]_D$ = -125).[71]

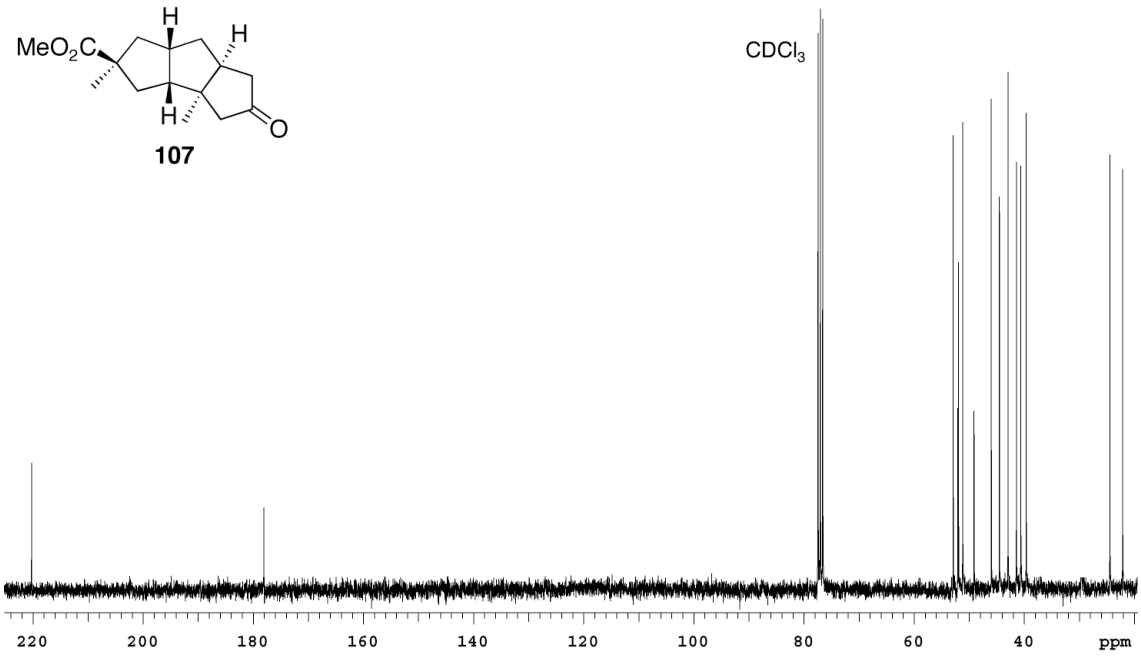


Figure 2.13: *300 MHz ^{13}C NMR spectrum of triquinane **107** (recorded in $CDCl_3$).*

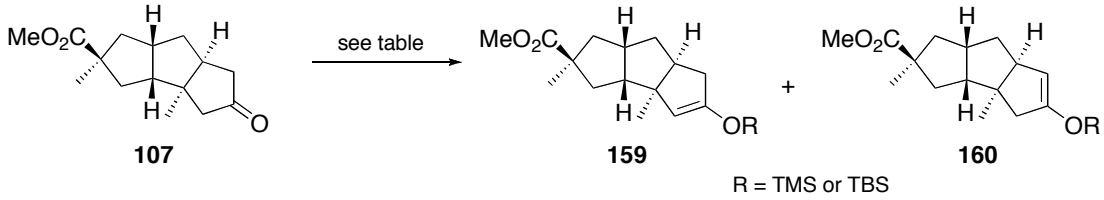
2.3.7 Completion of the syntheses of (+)-hirsutic acid and (-)-complicatic acid

With a successful route to the *cis:anti:cis* fused linear triquinane framework in hand, completion of the total syntheses of (+)-hirsutic acid and (-)-complicatic acid was pursued. The first step towards such ends was the oxidation of triquinane **107** to the corresponding enone, the

double bond of which would be used in the final stages of the synthesis to install the epoxide ring associated with the target natural products.

Initial attempts to introduce the carbonyl-conjugated olefin involved the use of the Saegusa oxidation protocol[99] (Scheme 2.19). It was anticipated that the angular methyl group would provide some control in the regioselective formation of the relevant silyl enol ether. However, a study of several bases and silylating agents (Table 2.2) showed only a modest selectivity for the desired enol ether **160**.

Table 2.2: *Formation of silyl enol ethers **159** and **160** using various bases and silylating agents.*

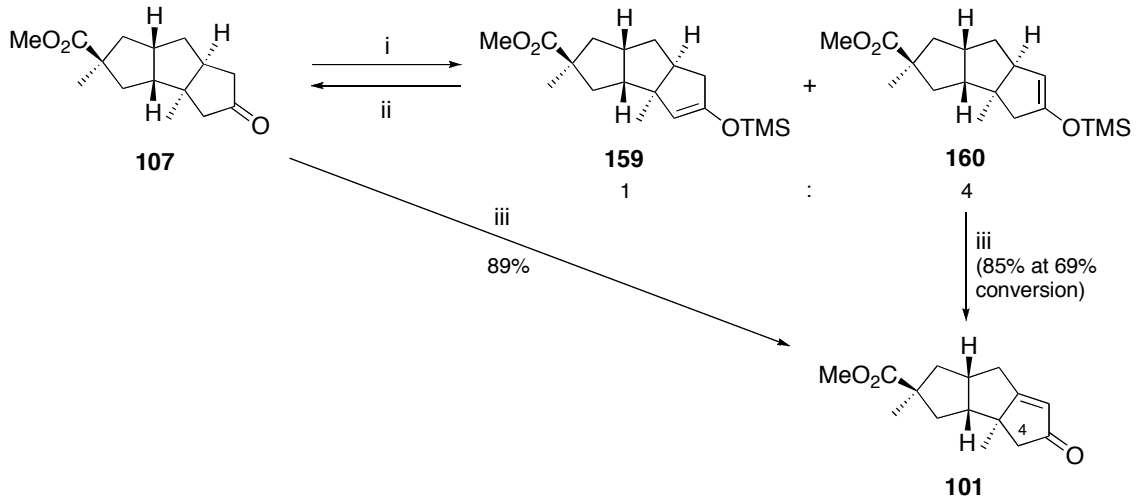


Entry	base	silylating agent	temperature	**159** (undesired)*	**160** (desired)*
1	LDA	TMSCl	-78 ºC	1	1.2
2	LiHMDS	TBSOTf	0 ºC	1	1.2
3	LiHMDS	TBSOTf	-78 ºC	1.1	1
4	LiTMP	TMSCl	-78 ºC	1	2.5
5	Lutidine	TMSOTf	0 ºC	No reaction	
6	Lutidine	TMSOTf	0 to 18 ºC	1	3.8
7	TBAF	ETSA	-78 to 0 ºC	1	7.0
8	TBAF	ETSA	18 ºC	1	4.0

* Ratios determined by ^{1}H NMR of the crude reaction mixture

Entries 7 and 8 define conditions reported by Crimmins *et al.* in their total synthesis of silphinene.[100] They had encountered, and solved, a similar problem of regioselective silyl enol ether formation using ethyl(trimethylsilyl)acetate (ETSA) and catalytic tetra-*n*-butylammonium fluoride (TBAF)[101] and thus reporting a 96:4 ratio of products in favour of the desired regioisomer. In the context of the present study this set of conditions was found to be the most selective. However, it proved difficult to achieve full consumption of the starting material and upon prolonged exposure to the reaction conditions the silyl enol ethers were found to hydrolyse

back to the starting ketone, presumably due to the catalytic quantities of TBAF present in the reaction mixture. The set of reaction conditions that was found to reliably be the most selective was 2,6-lutidine and trimethylsilyl triflate (TMSOTf) at 18 ºC (Entry 6), affording a *ca*. 4:1 ratio of products favouring the desired regioisomer. Because the undesired enol ether **159** could not be oxidised to the corresponding enone it was anticipated that it would be easily recycled to the starting ketone *via* acid hydrolysis. Accordingly, ketone **107** was converted into the corresponding a mixture of trimethylsilyl enol ethers which was then treated with $Pd(OAc)_2$ and *p*-benzoquinone in acetonitrile.[99] Aqueous work up resulted in hydrolysis of the extraneous trimethylsilyl enol ether, providing a chromatographically separable mixture of the starting ketone **107** (31% recovery) and the desired enone **101** (85% at 69% conversion). The most significant feature of the spectral data collected for enone **101** was the appearance of an olefinic signal at δ 5.68 in the ^{1}H NMR spectrum (Figure 2.14), which serves to confirm that installation of the double bond conjugated to a carbonyl moiety had taken place.



Scheme 2.19: *Reagents and conditions* (i) TMSOTf (3.0 mole equiv.), 2,6-lutidine (4.0 mole equiv.), CH_2Cl_2, 0 to 18 °C, 1 h; (ii) silica gel; (iii) $Pd(OAc)_2$ (2.0 mole equiv.), *p*-benzoquinone (1.0 mole equiv.), acetonitrile, 18 °C, 18 h; (iii) IBX (3.9 mole equiv.), *p*-TsOH•H_2O (0.3 mole equiv.), toluene/DMSO, 85 °C, 72 h.

This conversion could also be achieved using 2-iodobenzoic acid[102,103] (IBX) (Scheme 2.19). This procedure not only proved to be simpler, but to also be more efficient, affording enone **101** in 89% yield. The various conditions explored during the optimisation of this process revealed that four equivalents of IBX were required to achieve complete conversion and the presence of an acid source (*p*-TsOH•H_2O) was critical to the success of the reaction.

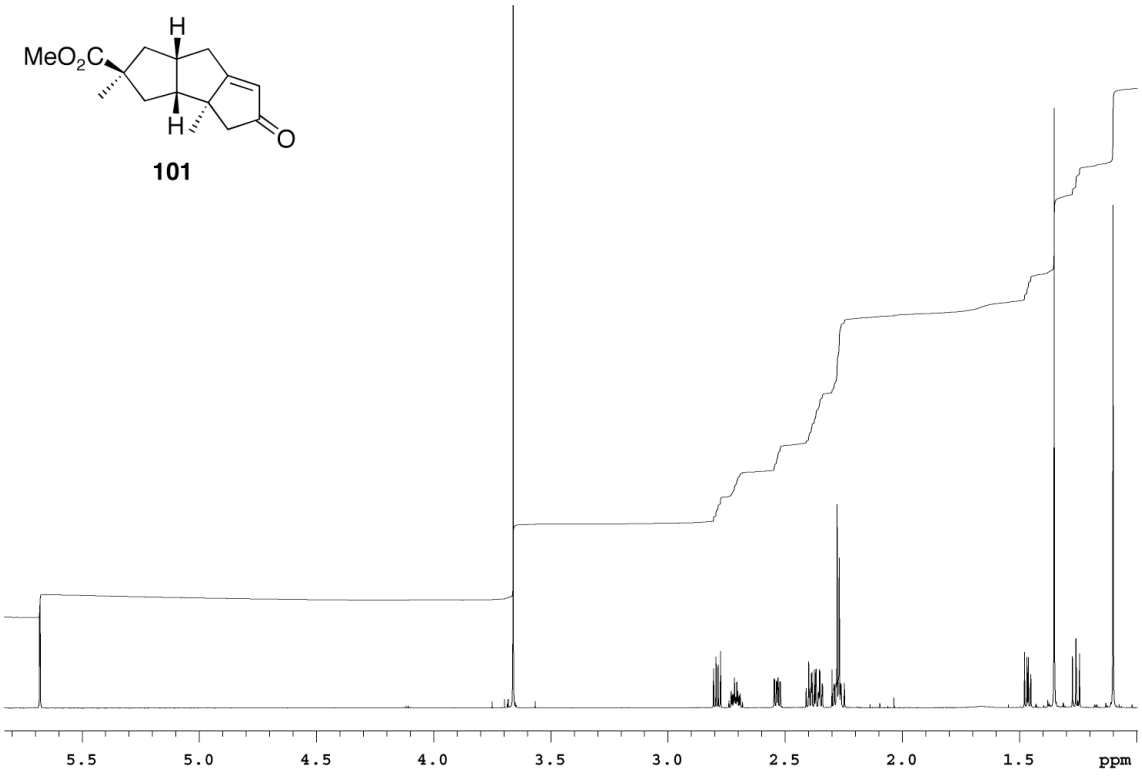
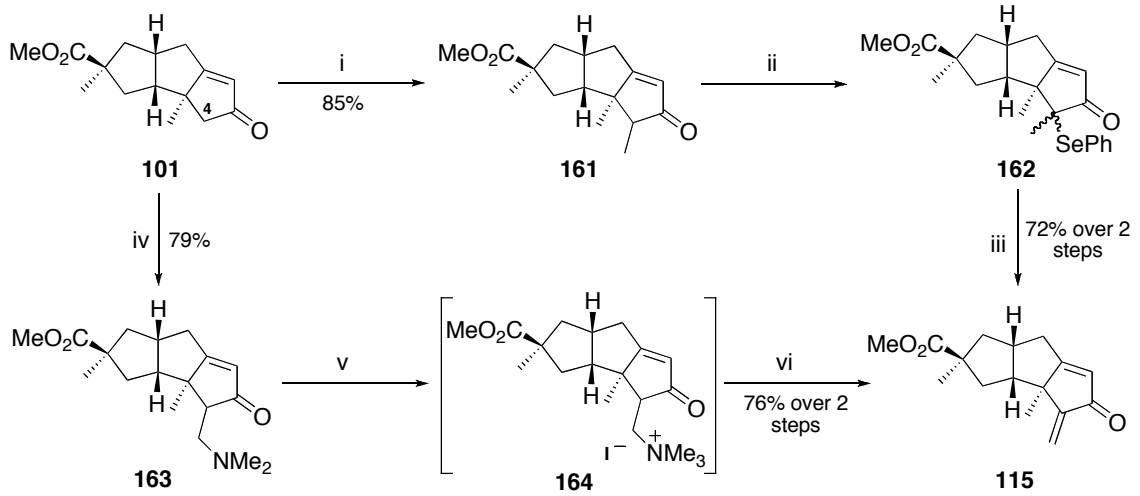


Figure 2.14: *800 MHz ^{1}H NMR spectrum of enone **101** (recorded in $CDCl_3$).*

It had been shown in previous syntheses of complicatic and hirsutic acids that the endocyclic olefin can be preferentially epoxidised in the presence of an exocyclic equivalent. This dictated that the best reaction sequence for completing the total syntheses would involve: (i) introduction of the α-methylene functionality, (ii) deprotection of the methyl ester and (iii) nucleophilic epoxidation of the endocyclic double bond. In the case of (+)-hirsutic acid these steps would be followed by stereoselective reduction of the carbonyl moiety within precursor (-)-**83**.

Two protocols for installing an exocyclic methylene at C4 of enone **101** were investigated (Scheme 2.20). The first of these was reported by Ikegami *et al.* in their total synthesis of (+)-hirsutic acid.[72] Thus, enone **101** was treated with LDA and methyl iodide to give a single diastereomeric form of α-methyl ketone **161**. The stereochemistry of this compound was not determined as it was presumed to be of little consequence. The crude product was then treated with LDA and phenylselenyl chloride to provide selenide **162** as a 1:2 mixture of diastereomers (once again the stereochemistry of the two compounds was not established). Hydrogen peroxide and acetic acid in THF were then used to oxidise selenide **162** to α-methylene enone **115** (51% over two steps from compound **160**). This yield could be improved upon by using sodium periodate as the oxidant and thus affording dienone **115** in 72% yield over the two steps. Unfortunately, product **115** was often contaminated with significant quantities of its chromatographically inseparable precursor **161**.

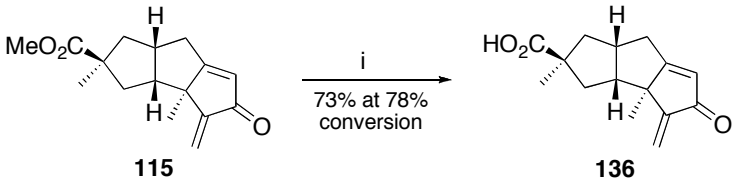


Scheme 2.20: *Reagents and conditions* (i) LDA (2.0 mole equiv.), MeI (10.0 mole equiv.), THF, −78 to 0 °C, 1.5 h; (ii) LDA (2.0 mole equiv.), PhSeCl (3.0 mole equiv.), THF, −78 to 18 °C, 1.5 h; (iii) $NaIO_4$ (5.0 mole equiv.), THF/H_2O/MeOH, 18 °C, 1 h; (iv) LiHMDS (1.5 mole equiv.), Eschenmoser's salt (3.0 mole equiv.), THF, −78 to 18 °C, 17 h; (v) MeI (12.0 mole equiv.), Et_2O/CH_2Cl_2, 18 °C, 16 h; (vi) basic alumina, CH_2Cl_2, 18 °C, 30 min.

In order to avoid the problems associated with the previous route, a new method for introducing the exocyclic methylene was investigated. Thus, the enolate of enone **101** was generated as described previously. However, it was now trapped with Eschenmoser's salt[104] ($H_2C{=}NMe_2^+\ I^-$) to afford the tertiary amine **163** (79%). Quaternization of amine **163** was achieved using methyl iodide and thus generating the corresponding methiodide salt **164**, which, on stirring with basic alumina, underwent a Hofmann-type elimination reaction to afford dienone **115** in 76% yield.[105]

The ^{1}H NMR spectrum of dienone **115** features two olefinic resonances at δ 5.89 and 5.17. Using HSQC experiments, it was determined that the former signal, which integrates for two protons, was due to both the proton of the endocyclic olefin and one of the protons of the exocyclic methylene. The one-proton singlet at δ 5.17 was assigned to the other proton of the terminal methylene. The ^{13}C NMR spectrum exhibited four signals in the olefinic region, consistent with the presence of two double bonds in the molecule. The medium strength absorption band appearing at 1648 cm^{-1} in the IR spectrum is characteristic of a carbonyl-conjugated and exocyclic alkene.

With dieneone **115** in hand, the next step required was the hydrolysis of the methyl ester to the carboxylic acid. This was achieved using LiI in refluxing DMF to afford, after acidic work-up, crystalline dienone acid **136** in 73% yield (at 78% conversion).



115 **136**

Scheme 2.21: *Reagents and conditions* (i) LiI (15.0 mole equiv.), DMF, reflux, 34 h.

The spectral data, including optical rotation, obtained for this material matched those reported by Greene *et al.*[71] Final confirmation of structure was obtained by single-crystal X-ray analysis (Figure 2.15, Appendix 8).

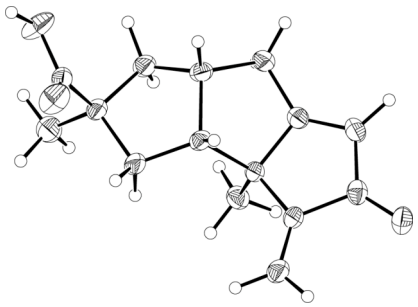
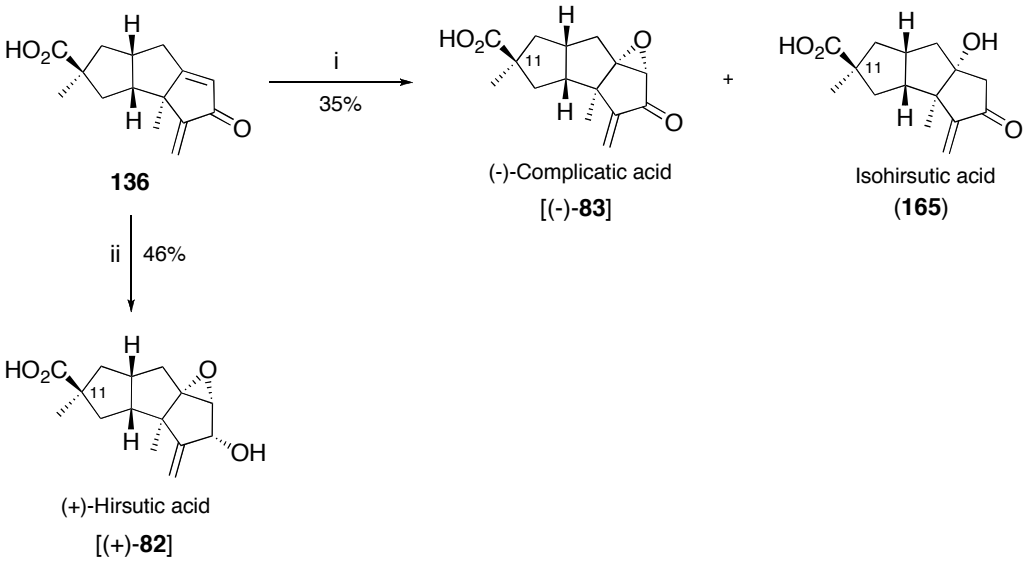


Figure 2.15: *Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of dienone acid **136**.*

The synthesis of (-)-complicatic acid [(-)-**83**] was completed by regio- and stereo-selective nucleophilic epoxidation of compound **136** (Scheme 2.22). This was achieved using a three-fold excess of alkaline hydrogen peroxide in MeOH at -50 to -36 °C to afford (-)-complicatic acid, as an oil, in a modest 35% yield.[72] Various attempts to improve upon this outcome were unsuccessful. For example, the use of higher reaction temperatures and/or additional quantities of alkaline hydrogen peroxide led to complex mixtures of material which appeared to contain significant quantities of a bis-epoxide as judged by mass spectral analysis of the crude reaction mixture. A slightly better outcome was achieved when the nucleophilic epoxidation process was followed by immediate treatment of the crude reaction mixture with sodium borohydride.[71] By such means (+)-hirsutic acid [(+)-**82**] could be obtained, after chromatographic purification, in 46% yield and as a microcrystalline solid (Scheme 2.22).



Scheme 2.22: *Reagents and conditions* (i) H_2O_2 (3.0 mole equiv.), NaOH (3.0 mole equiv.), MeOH/H_2O, −50 to -36 °C, 1 h; (ii) a) H_2O_2 (3.0 mole equiv.), NaOH (3.0 mole equiv.), MeOH/H_2O, −35 °C, 4 h; b) $NaBH_4$ (19.0 mole equiv.), EtOH, −35 to 0 °C, 30 min.

The spectral data obtained on products (+)-**82** and (-)-**83** are fully consistent with the data reported for the natural products. Thus, the 300 MHz ^{1}H NMR spectrum of (-)-complicatic acid [(-)-**83**] (Figure 2.16) features resonances at δ 6.08 and 5.30 that suggest the exocyclic methylene is still in place. The appearance of a singlet at δ 3.44 can be attributed to the methine proton of the newly installed epoxide. The signal due to the carboxylic acid proton was not observed. Unfortunately, and despite purification twice using silica gel column chromatography, compound (-)-**83** was found to be contaminated with a related compound (*ca.* 10%). The resonances associated with this compound in the ^{1}H NMR spectra are consistent with those reported for isohirsutic acid[60] (**165**) (Scheme 2.22), which was first reported by Comer *et al*.[52] and later synthesised by Lansbury and co-workers.[60] Matsumoto *et al.* also observed the *O*-methylated derivative of isohirsutic acid as a major by-product (20%) of their synthesis of complicatic acid.[61] The EI mass spectrum of compound (-)-**83** displays a molecular ion at *m/z* 262, and accurate mass measurement on this species established the molecular formula of the compound as $C_{15}H_{18}O_4$. Finally, the specific rotation obtained for compound (-)-**83** was $[\alpha]_D$ = -77 (*c* 0.3 in $CHCl_3$), which compares favourably with the value of $[\alpha]_D$ = -79 (*c* 1.1 in $CHCl_3$) recorded for the originally isolated natural product.[54]

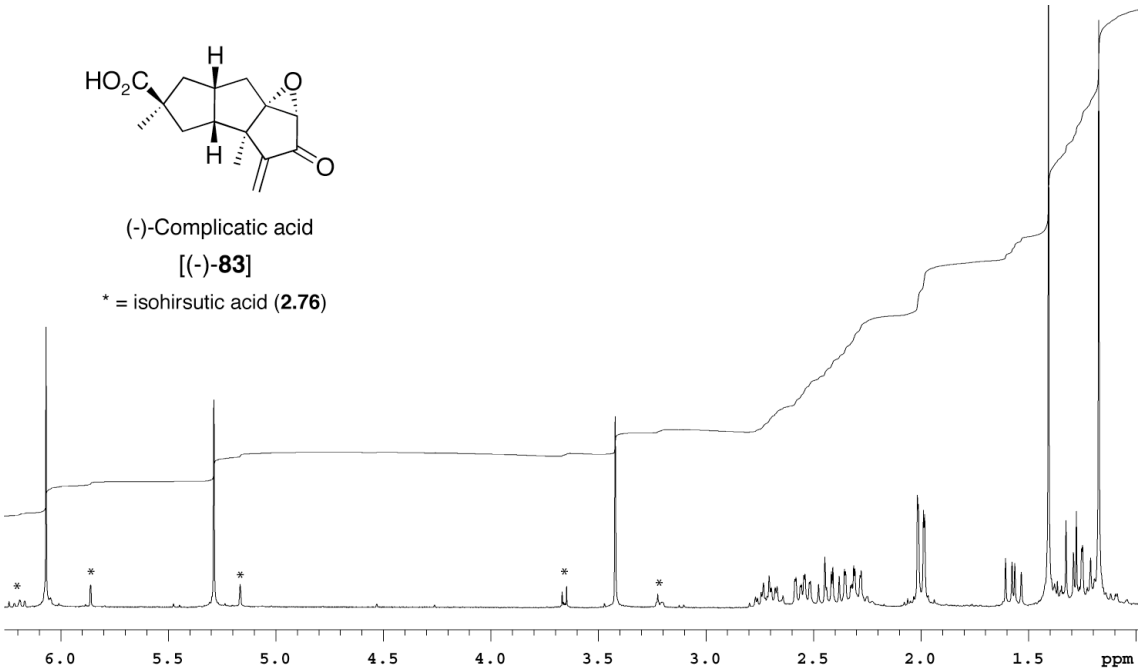


Figure 2.16: *300 MHz ^{1}H NMR spectrum of (-)-complicatic acid [(-)-**83**] (recorded in $CDCl_3$).*

Both the ^{1}H NMR (Figure 2.17) and the ^{13}C NMR spectra (Figure 2.18) of (+)-hirsutic acid [(+)-**82**] display all of the expected features and are in full accord with the data reported for the natural product. The EI mass spectrum displays a molecular ion at *m/z* 264 and a fragment ion at *m/z* 247 resulting from the loss of a hydroxyl group. An accurate mass measurement on the molecular ion confirmed its composition as $C_{15}H_{20}O_4$. The specific rotation obtained for compound (+)-**82** was +113 (*c* 0.2, $CHCl_3$), which is in good agreement with the value observed for the natural product [+116 (*c* 1.05, $CHCl_3$)][54] The melting range of 168–171 °C compares less favourably with that obtained for the natural product (178.5–180 °C).[54] Nevertheless, other synthetically-derived samples have melting points closer to this value, for example, Ikegami *et al.* reported a melting point of 170 °C.[72]

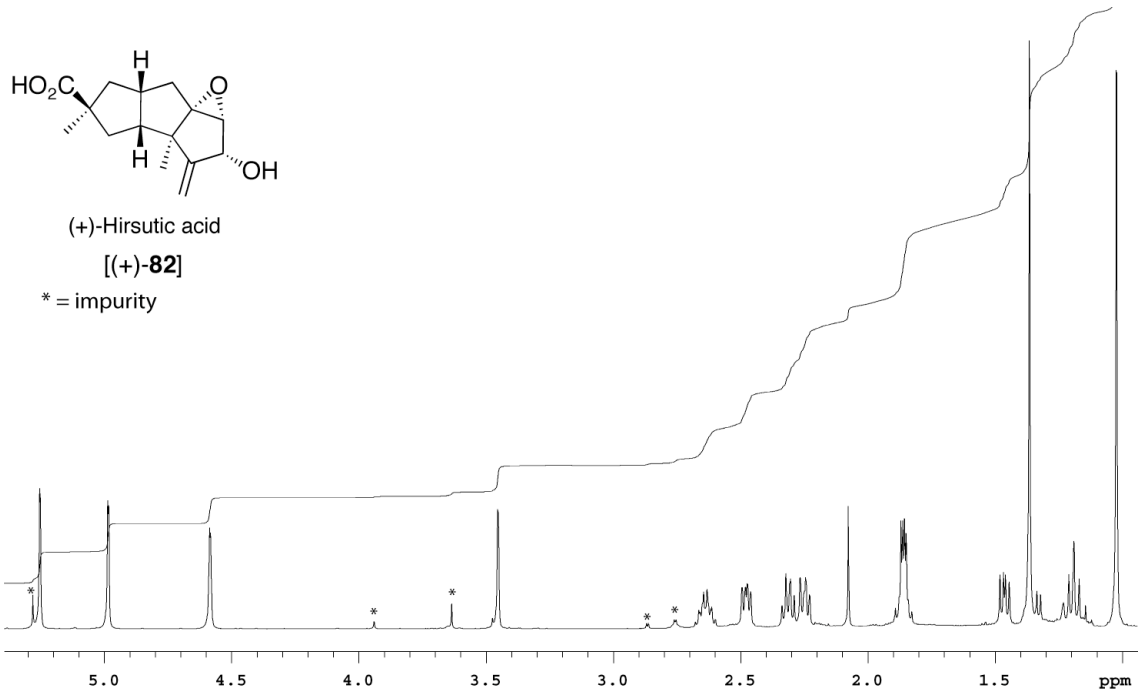


Figure 2.17: *600 MHz ^{1}H NMR spectrum of (+)-hirsutic acid [(+)-**82**] (recorded in $CDCl_3$).*

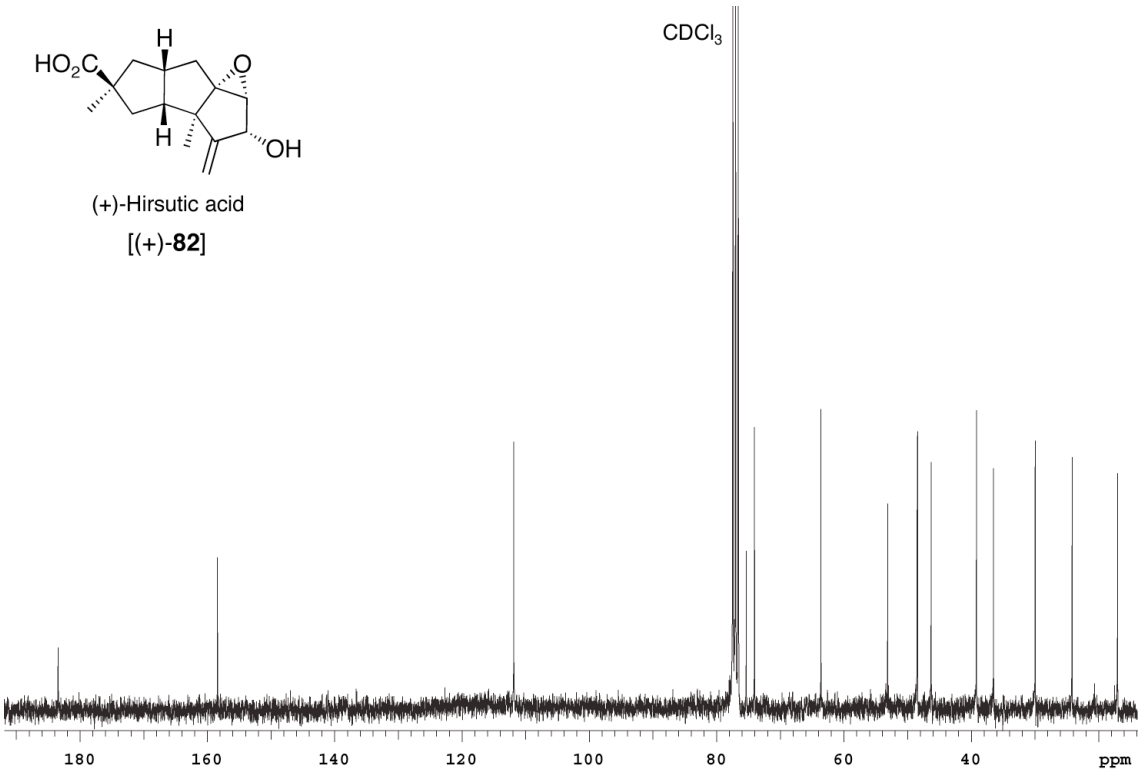


Figure 2.18: *75 MHz ^{13}C NMR spectrum of (+)-hirsutic acid [(+)-**82**] (recorded in $CDCl_3$).*

2.4 Conclusions and Future Work

In the work described in this Chapter, *c*-DHC **35**, derived from microbial oxidation of toluene, has been converted into the natural products (+)-hirsutic acid and (-)-complicatic acid. This nineteen-step sequence proceeded in overall yield of *ca*. 3% and is noteworthy in that seven of the fifteen carbons in the title natural products originate from the cheap and abundant toluene starting material. When combined with the studies of Harfoot *et al.*,[42,43] these results demonstrate that by controlling the facial selectivity of the Diels–Alder reactions involving diene **35,** either enantiomeric form of the linear triquinane framework can be obtained. Furthermore, the reaction sequences described in this Chapter allow for the stereoselective introduction of functionality at most positions on the triquinane framework. Such control is particularly important given the continued isolation of new and interesting linear triquinoid type natural products, many of which display attractive biological profiles.[106] Figure 2.19 presents some examples of triquinoid natural products that it is anticipated can be synthesised using the methodology described here. These compounds all exhibit antibacterial activity against a range of Gram-positive and Gram-negative bacteria. However, in addition they show varied and interesting biological profiles. For example phelladonic acid$^{\Sigma}$ [(-)-**142**] is highly cytotoxic,[107] desoxyhypnophilin (**166**) shows significant antimalarial activity,[108] while pleurotellol (**168**) has been demonstrated to act as a plant growth inhibitor.[109] Creolophin E (**169**) has been isolated recently and shown to inhibit the growth of various cancer cell lines.[108]

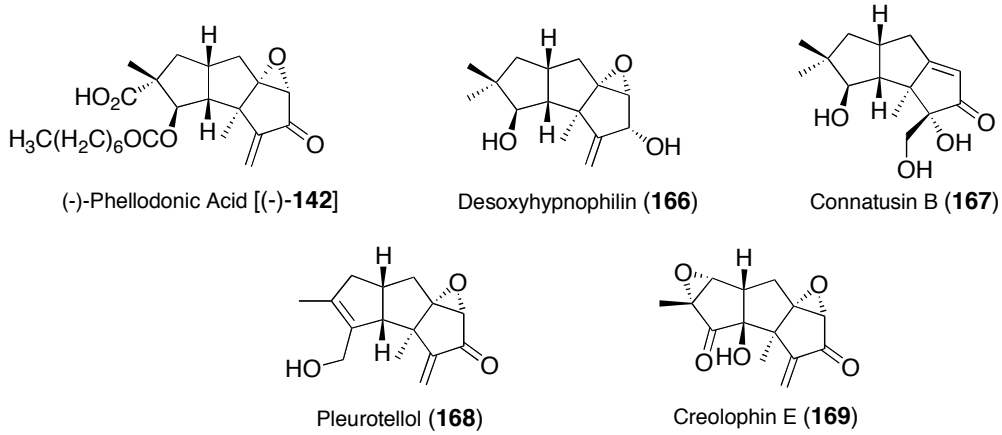


Figure 2.19: *A selection of linear triquinane natural products with interesting biological properties.*

Σ A total synthesis of phelladonic acid has since been completed in these laboratories utilising the chemistry described in this Chapter.[78]

CHAPTER THREE

Intramolecular Diels-Alder Cycloaddition Reactions of cis-*1,2-Dihydrocatechols*

3.1 Introduction

3.1.1 Research objectives

As described in Chapter 1, both *inter*- and *intra*-molecular Diels-Alder cycloaddition reactions of *c*-DHC[ß] derivatives have been reported.[7,10] However, while the *inter*-molecular variant (DA) has found extensive use in enantioselective syntheses,[37,38,40,73,110-112] the analogous *intra*-molecular (IMDA) process has been used to a lesser extent.[30,31] There are a number of reasons for this. Firstly, DA cycloaddition reactions can be performed directly on *c*-DHCs, whereas their IMDA counterparts require prior attachment of a dienophilic tether. Due to the propensity of *c*-DHCs to aromatise this can be a challenging task. Secondly, DA cycloaddition reactions of *c*-DHCs are known to be completely *endo*-selective and by employing either the protected or the unprotected derivatives the diastereofacial selectivity can be controlled effectively. In contrast, the selectivity profiles of the corresponding IMDA reactions have not been well characterised.

The work described in this Chapter was carried out with the aim of better characterising the IMDA cycloaddition reactions of *c*-DHCs and in order to develop new synthetic routes to sesquiterpenoid natural products. Thus, the specific objectives were:

(i) To design precursors in which the dienophilic tether was positioned on the *c*-DHC framework such that a wide range of carbocyclic frameworks could be accessed.

(ii) To develop coupling methods in order to tether the dienophilic moiety to the *c*-DHC framework in high yields.

(iii) To characterise the stereoselectivity (*endo vs exo*) of the IMDA cycloaddition reactions of *c*-DHCs.

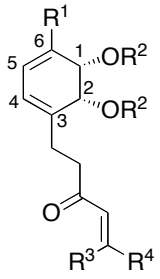
[ß] This abbreviation for '*cis*-1,2-dihydrocatechol' is used throughout this Chapter.

(iv) To develop methods for controlling the diastereofacial (*syn vs anti*) selectivity of the IMDA cycloaddition reactions of *c*-DHCs.

3.2 Intramolecular Diels-Alder (IMDA) Precursors

3.2.1 Precursor design

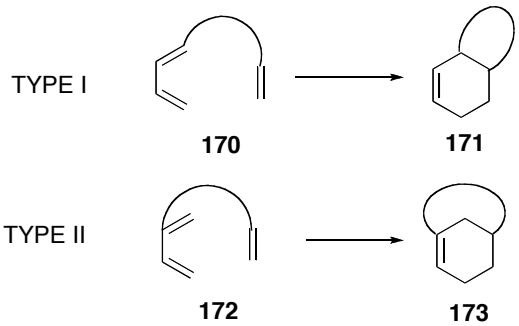
This Section outlines the considerations that influenced the design of the proposed IMDA precursors (Figure 3.1). Ultimately, a precursor that included a 5-membered tether with an internal ketone-activating group attached at the 3-position of the *c*-DHC framework was identified as the most appropriate substrate for an initial study of the title reactions.



85

Figure 3.1*: General structure of IMDA precursors to be investigated.*

There are two distinct types of IMDA cycloaddition reaction.[19,113,114] These differ in the position at which the dienophile is tethered to the diene (Scheme 3.1). In Type I IMDA reactions the dienophile is tethered at the terminus of the diene, whereas in the Type II equivalent the dienophile is tethered at an internal position of the diene. Because 3-substituted *c*-DHC derivatives are more readily available than the corresponding 4- or 5-substituted derivatives, this work focused on Type I IMDA cycloaddition reactions in which the dienophile is tethered at the 3-position of the relevant *c*-DHC framework.



Scheme 3.1: *The two classes of IMDA cycloaddition reactions.*

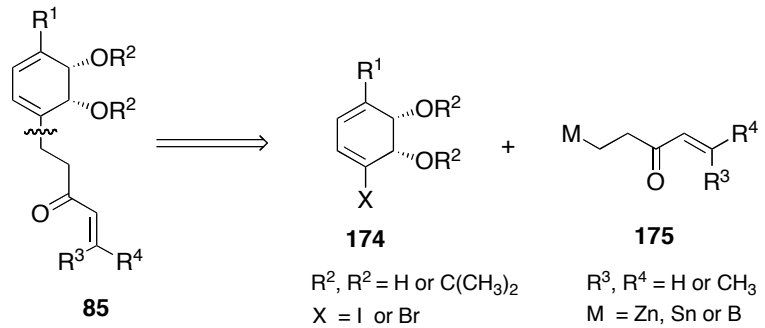
It is worth noting that when the dienophile is tethered through the C-1 or C-2 hydroxyl groups within the *c*-DHC, the facial selectivity of the IMDA cycloaddition reaction is completely constrained.[31,32] In contrast, with the tether attached at the 3-position, the IMDA cycloaddition reaction could potentially occur at either face of the diene such that with the use of different alcohol protecting groups (R^2), it might be possible to control the diastereofacial (*syn*/*anti*) selectivity of these processes.

The stereoselectivities of IMDA cycloaddition reactions can be influenced by the position of electron-withdrawing group that serves to activate the dienophile in a normal electron-demand Diels-Alder reaction.[113] It may be positioned internally, within the tether, or at the terminus of the dienophile. It was decided that an internal activating group, such as a ketone, would be the most versatile as this would allow varied substitution at the terminus of the dienophile (R^3/R^4) as well as enabling further functionalisation of the newly formed ring.

The reason for choosing a five-membered tether in the initial studies derives from the expectation that the resulting adducts would provide access to a wide variety of sesquiterpenoid natural products.

3.2.2 Retrosynthetic analysis

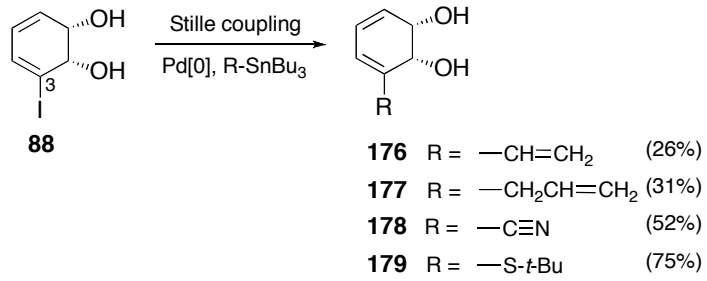
Owing to the instability of the *c*-DHC moiety, microbial oxidation of the aromatic ring should, ideally, be the last step in the synthesis of these precursors. However, the substrate range for the enzymatic oxidation is limited by the size and nature of the substituents on the benzene ring.[11] The proposed strategy, therefore, relies on a late-stage union of the *c*-DHC fragment (**174**) and the tether to which the dienophilic residue is already attached (**175**) (Scheme 3.2).



Scheme 3.2: *Retrosynthetic analysis of IMDA precursors.*

3.2.3 Previous studies on C-C bond forming reactions of *cis*-1,2-dihydrocatechols

Several groups have shown that it is possible to prepare a range of *c*-DHCs that are substituted in the 3-position *via* metallation of readily available 3-halogenated derivatives.[27,115-119] For example Boyd *et al*. have demonstrated that 3-iodo-*c*-DHC **88** readily participates in palladium-catalysed Stille cross-coupling reactions with a range of organotin reagents to afford a series of 3-substituted derivatives in yields from 11-75% (Scheme 3.3).[115,116] The modest yields sometimes observed are attributed to the instability of the products to column chromatography. However, this procedure has an important advantage, namely the ability to effect direct substitution without needing to protect (then deprotect) the diol moiety.

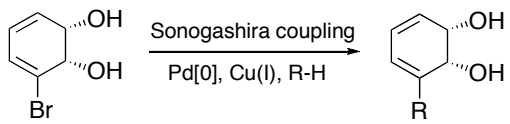


88

176 R = —CH=CH$_2$ (26%)
177 R = —CH$_2$CH=CH$_2$ (31%)
178 R = —C≡N (52%)
179 R = —S-*t*-Bu (75%)

Scheme 3.3: *Examples of Stille cross-coupling reactions of unprotected 3-iodo-*c*-DHC (**88**).*

Although Boyd *et al.* found the corresponding bromo-derivative to be less reactive in the Stille cross-coupling reactions (substitution was only observed with activated organotin reagents and gave lower yields),[115] Hudlicky and co-workers demonstrated that 3-bromo-*c*-DHC readily participates in the Sonogashira cross-coupling reaction to give alkynyl-substituted derivatives in good yields.[117] However, only three examples of such a process have been reported to date (Scheme 3.4).

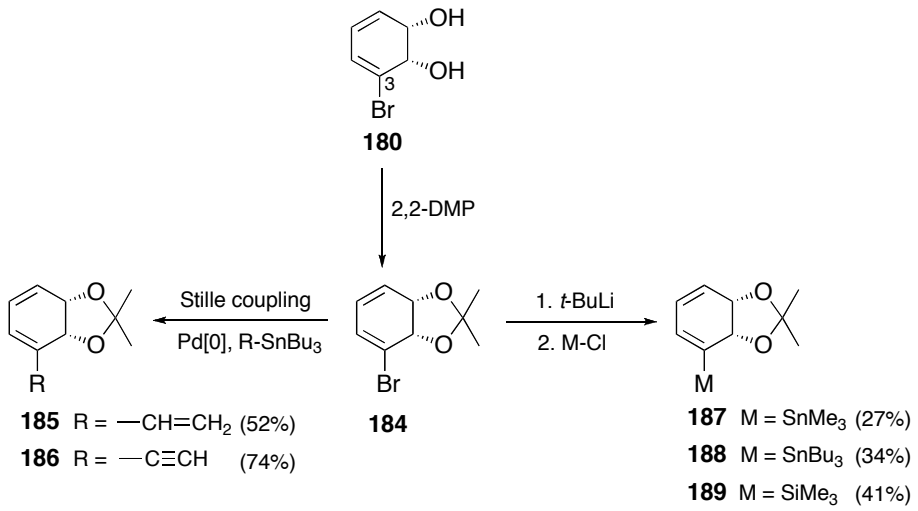


180

181 R = —C≡C—TMS (78%)
182 R = —C≡C—Ph (91%)
183 R = —C≡C—(CH$_2$)$_3$CH$_3$ (70%)

Scheme 3.4: *Sonogashira coupling reactions of unprotected 3-bromo-*c*-DHC (**180**) with various terminal acetylenes.*

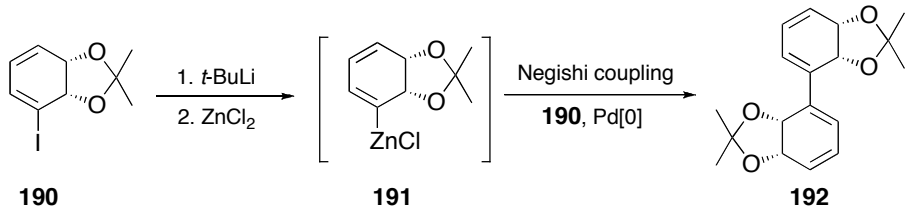
Recognising that acetonide-protected derivatives of *c*-DHCs are significantly more stable and thus more likely to produce high yields of coupling products, Ley *et al*. prepared a variety of 3-substituted compounds from acetonide **184** (Scheme 3.5).[27]



Scheme 3.5: *Examples of Stille couplings and metallations of acetonide-protected 3-bromo-*c*-DHC* ***184****.*

Acetonide **184** was found to readily participate in Stille cross-coupling reactions with vinylbutyltin and ethynyltributyltin and so afford the corresponding 3-substituted products (compounds **185** and **186**, respectively) in better yields than those observed for the equivalent reactions involving diol **88**. It was also found that compound **184** could be metallated with *tert*-butyllithium (*t*-BuLi) and trapped *in situ* with trimethyltin chloride or bistributyltin to generate the corresponding stannylated compounds **187** and **188** in 27% and 34% yields, respectively. Both of these compounds were subsequently used in Stille cross-coupling reactions. Finally, the trimethylsilyl derivative **189** was also generated by metallation followed by trapping with trimethylsilyl chloride. However, this silylated product was not used in any cross-coupling reactions.

In a single example, acetonide-protected 3-iodo-*c*-DHC **190** has also been metallated using *tert*-butyllithium and the resulting lithiospecies transmetallated using zinc chloride. The organozinc species so formed was then subjected to Negishi cross-coupling with a further equivalent of iodide **190** to afford dimer **192** in 40% yield (Scheme 3.6).[119]



Scheme 3.6: *Negishi coupling of acetonide-protected 3-iodo-*cis*-1,2-dihydrocatechol **190**.*

Although the work outlined in this Section provides precedent for the union of the *c*-DHC moiety and the dienophilic tether *via* a cross-coupling reaction, there were certain limitations to such processes that needed to be overcome. Firstly, these reactions were generally low-yielding, which is mainly due to the instability of the *c*-DHCs themselves. This problem can be minimised, however, by using the corresponding acetonide derivative. Secondly, the successful couplings observed to this point generally use highly reactive coupling partners such as vinyl and allyl stannanes. In contrast, the coupling partners that would need to be used in the synthesis of the desired IMDA precursors, specifically alkyl-based reagents, will be considerably less reactive in these cross-coupling reactions.

3.3 Synthesis of IMDA Precursors *via* Palladium-Catalysed Cross-Coupling Reactions

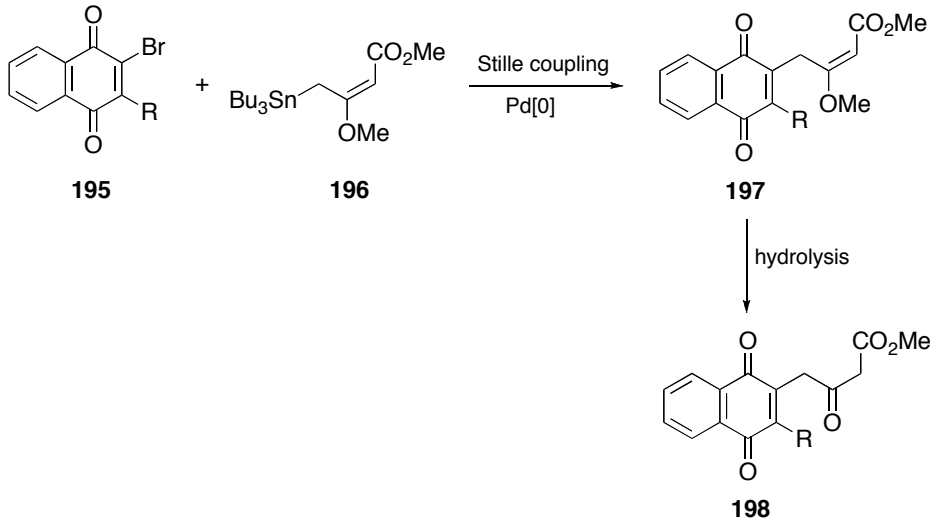
3.3.1 The Stille cross-coupling approach

Because Stille cross-coupling reactions have been shown to be successful with both protected and unprotected *c*-DHCs, the first approach to the synthesis of the IMDA precursors utilised this reaction. Following the proposed retrosynthetic analysis (Scheme 3.2, page 63), it was envisioned that alkylstannane **193** (Figure 3.2) could be engaged in a cross-coupling reaction with 3-iodo-*c*-DHC. However, there is limited literature precedent regarding the use of alkylstannanes as coupling partners in Stille cross-coupling reactions. On the other hand, allylstannanes readily participate in such cross-coupling reactions, and there are numerous examples of such reactions in the literature.[120] Accordingly, silyl enol ether **194** was proposed as a more appropriate coupling partner than congener **193**.

193 **194**

Figure 3.2: *Proposed organostannaes for use in the Stille cross-coupling reaction.*

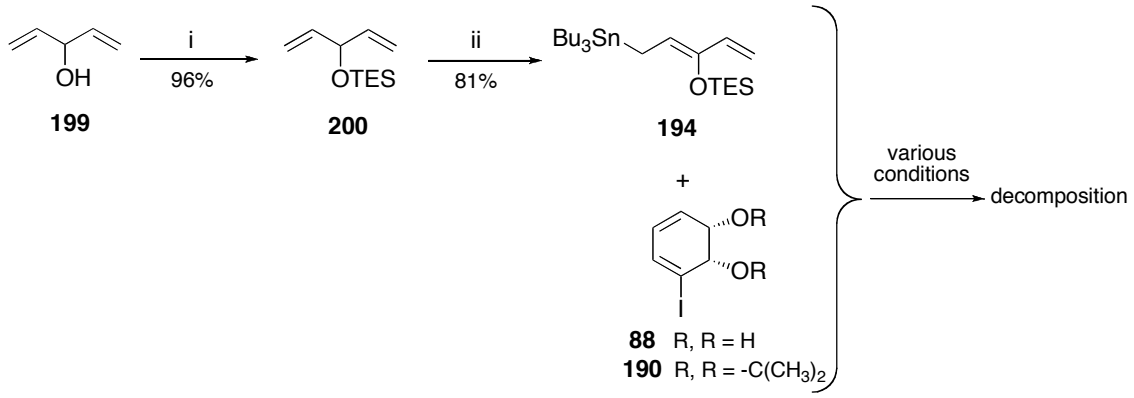
It was envisioned that the triethylsilyl enol ether moiety would be stable under the reaction conditions and that the coupling product could then be hydrolysed to afford the desired vinyl ketone functionality. A similar strategy has been used by Krohn and co-workers who coupled alkenyl bromide **195** with an allyl stannane possessing a methyl enol ether (**196**) to obtain compound **197**. The enol ether moiety within the coupled product was then hydrolysed to afford β-keto-ester **198** (Scheme 3.7).[121]



195 **196** **197** **198**

Scheme 3.7: *Stille cross-coupling of allyl stannane **196** and subsequent hydrolysis of the methyl enol ether to the corresponding ketone.*

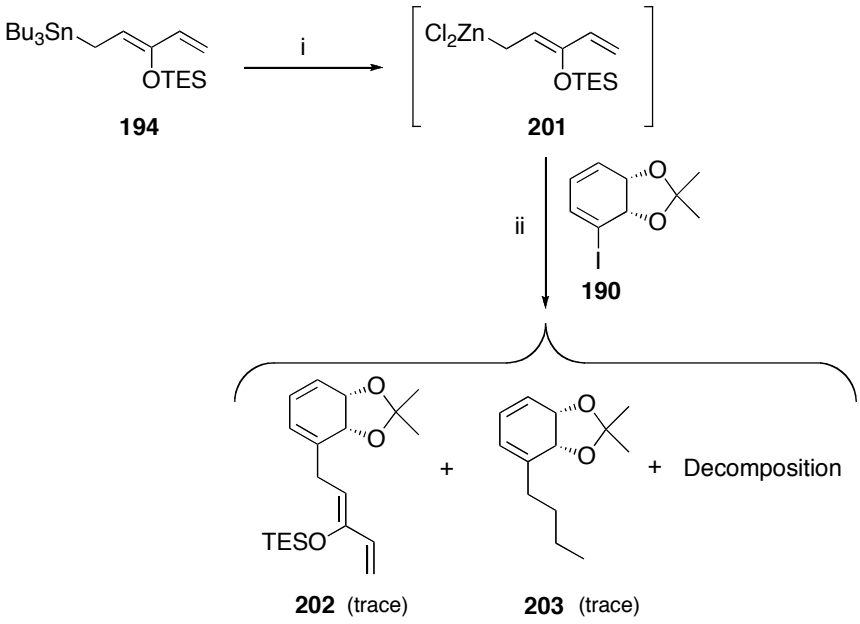
In an effort to implement such ideas, allyl stannane **194** was synthesised using the protocols of Fuchs and co-workers (Scheme 3.8).[122] Thus, commercially available 1,4-pentadien-3-ol (**199**) was protected as the corresponding triethylsilyl ether **200** and this was treated with *sec*-butyllithium to generate a symmetrical pentadienyl lithium derivative.[123] This anion was then quenched with tributylstannyl chloride to afford, regioselectively, the γ-substituted allyl stannane **194**. The spectroscopic data derived from this material were fully consistent with those reported in the literature.[122] Disappointingly, all attempts to engage this material in Stille cross-coupling reactions with 3-iodo-*c*-DHC (**88**), or the corresponding acetonide **190**, only resulted in decomposition of the staring materials.



Scheme 3.8: *Reagents and conditions* (i) imidazole (1.2 mole equiv.), TESCl (1.1 mole equiv.), DMF, 0 to 18 °C, 1 h; (ii) *s*-BuLi (1.1 mole equiv.), *n*-Bu_3SnCl (1.1 mole equiv.), THF, -78 °C, 1.5 h.

3.3.2 The Negishi cross-coupling approach

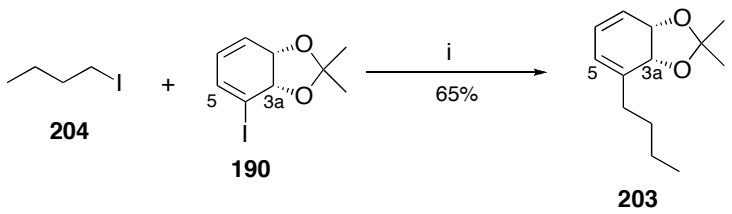
Following the abovementioned failure of the Stille reactions, an alternative cross-coupling procedure was sought. Pimm and co-workers have shown that an unreactive organostannane can be converted into a more active organozinc reagent, which readily participates in a Negishi cross-coupling reaction.[124] Accordingly, allyl stannane **194** was treated with *n*-butyllithium (to effect a Sn/Li-exchange) then $ZnCl_2$ (to generate the corresponding organozinc compound **201**). A mixture of acetonide **190** and $Pd(PPh_3)_4$ was added to the reaction mixture that was then heated at 60 ºC overnight, cooled and subjected to the usual work-up procedures. Although significant decomposition of both coupling partners was observed, two products were isolated, albeit in small quantities. These were tentatively assigned, through ^{1}H NMR and EI mass spectroscopic analysis, as compounds **202** and **203** (Scheme 3.9).



Scheme 3.9: *Reagents and conditions* (i) a) *n*-BuLi (1.0 mole equiv.), THF, -78 ºC, 15 min; b) $ZnCl_2$ (1.1 mole equiv.), THF, -78 to 18 °C, 1 h; (ii) **190** (1.1 mole equiv.), $Pd(PPh_3)_4$ (13 mol%), THF, 18 ºC, 16 h.

While compound **202** is the desired product of the Negishi cross-coupling reaction, compound **203** is assumed to arise from Li/Zn transmetallation of unreacted *n*-butyllithium and subsequent cross-coupling of the resultant organozinc species with the *c*-DHC. Interestingly, although the reaction was attempted with a variety of lithium and zinc sources, silyl enol ether **202** was only ever obtained in trace amounts. In contrast, it could be shown, in a control experiment, that the organozinc reagent derived from *n*-butyllithium readily participates in the Negishi cross-coupling reaction with iodide **190** at room temperature to give significant amounts (not quantified) of compound **203**.

Unlike the Stille cross-coupling reactions, there are many examples of Negishi cross-coupling reactions with alkyl metal species. In fact, alkyl zinc reagents have proven to be superior to any other alkyl metal species that have been examined to date.[125] In order to test the suitability of an alkyl zinc reagent derived from an alkyl halide in this synthetic route, a model reaction was conducted using commercially available 1-iodobutane **204**. Thus, this material was subjected to lithium-for-halogen exchange using *tert*-butyllithium at -78 ºC and the resulting anion was quenched by using a THF solution of anhydrous $ZnCl_2$ to generate, after warming to 18 ºC, the desired organozinc species. Subsequent addition of a mixture of iodide **190** and $Pd(PPh_3)_4$ afforded compound **203** in 65% yield (Scheme 3.10).



Scheme 3.10: *Reagents and conditions* (i) a) *t*-BuLi (2.2 mole equiv.), THF, -78 °C, 20 min; b) $ZnCl_2$ (1.1 mole equiv.), THF, -78 to 18 °C, 1 h; c) **190** (1.0 mole equiv.), $Pd(PPh_3)_4$ (10 mol%), THF, 18 ºC, 2 h.

There are several noteworthy features associated with the ^{1}H NMR spectrum of compound **203** (Figure 3.3) that proved useful for identifying the presence of coupled products in the ^{1}H NMR spectra of crude reaction mixtures arising from related processes. Thus, the signals assigned to the protons at C5 (δ 5.72) and C3a (δ 4.54) in the product are located further up-field than the corresponding ones arising from the starting material (δ 6.66 and 4.73, respectively). Furthermore, a new two-proton multiplet, located at δ 2.23, can be attributed to the allylic methylene of the newly introduced butyl-chain. The remainder of the spectrum is in accord with the assigned structure. The EI mass spectrum displays a molecular ion at *m/z* 208 and an accurate mass measurement on this species established that it was of the expected molecular composition, *viz.* $C_{13}H_{20}O_2$. A specific rotation of $[\alpha]_D = +125$ (*c* 1.6, $CHCl_3$) was observed for this compound.

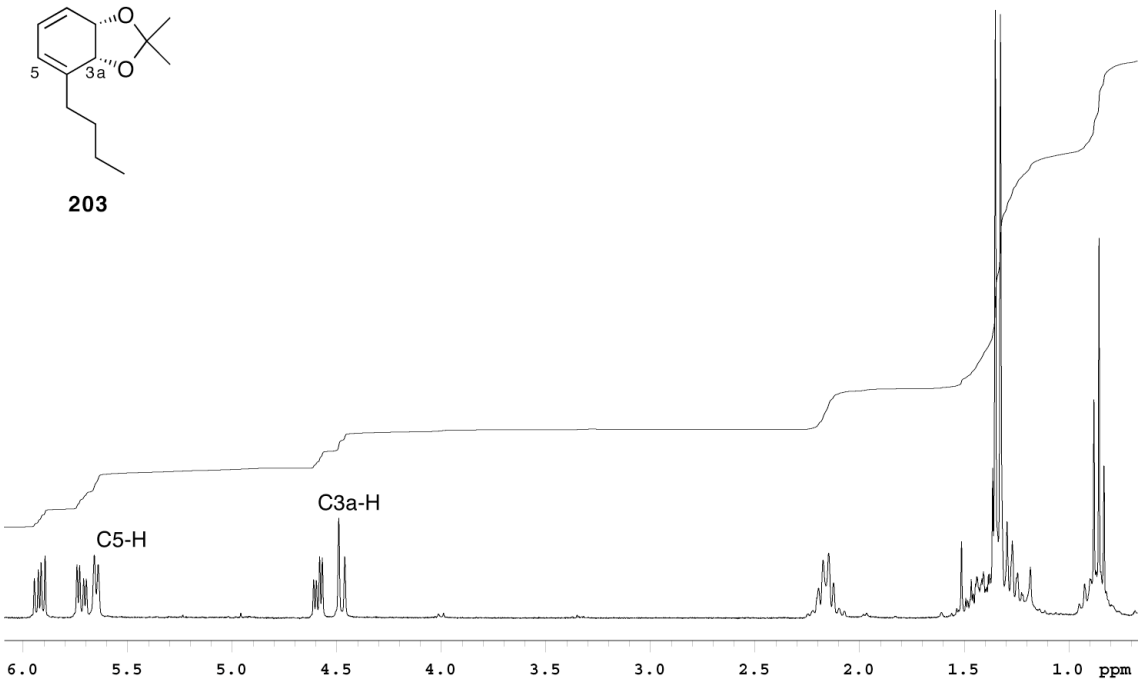
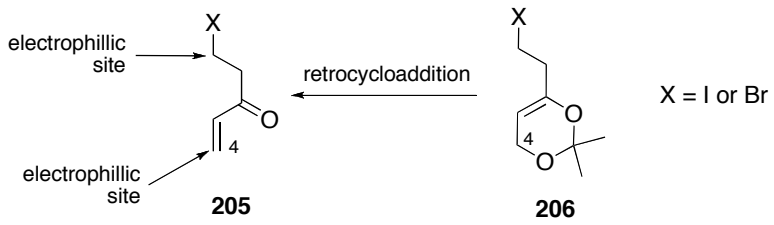


Figure 3.3: *300 MHz ^{1}H NMR spectrum of coupled product **203** (recorded in $CDCl_3$).*

With a procedure for the alkylation of acetonide **190** in hand, attention was turned towards the design and synthesis of suitable alkyl halides for use in the Negishi cross-coupling reaction in order to access substrates required for the proposed IMDA reactions. Such syntheses are described in the following Sections.

3.3.3 Halo-dioxin 206 as an β-haloethyl vinyl ketone equivalent

Any synthesis of the desired IMDA precursors using the abovementioned Negishi cross-coupling protocol requires the use of β-haloethyl vinyl ketone **205** (Figure 3.4), or an equivalent compound, as a precursor to the proposed alkylzinc coupling partner (**175**, M = Zn) depicted in the retrosynthetic analysis (Scheme 3.2, page 63). Although the synthesis of β-chloroethyl vinyl ketone has been reported in the literature several times,[126] there are no protocols describing the preparation of the corresponding bromo- or iodo-derivatives required for the work presented here. This is probably due to the inherent instability of these compounds as they would be expected to be prone to polymerisation under basic conditions and the β-substituent is also likely to be highly susceptible to elimination. Moreover, the lack of selectivity between the two electrophilic sites is likely to restrict the types of reactions they could engage in. To circumvent these problems, Funk and co-workers introduced dioxin **206** as a β-haloethyl vinyl ketone equivalent (Scheme 3.11).[127] In that work, it was demonstrated that dioxin **206** could be alkylated on the halogen-bearing centre then, *via* a cycloreversion process involving the 1,3-dioxin, the enone moiety could be revealed for further reaction.



Scheme 3.11: *Dioxin **206** as a β-haloethyl vinyl ketone (**205**) synthon.*

There are several features of dioxin **206** that made it an attractive coupling partner for use in the present work. These are:

(i) Protection of the carbonyl moiety in the suggested manner should allow for the use of *tert*-butyllithium to affect the lithium-for-halogen exchange (this is required prior to formation of the organozinc species).

(ii) It was envisioned the cycloreversion process would be followed, *in situ,* by the intramolecular Diels-Alder reaction.[Ω] This would remove the need to isolate and handle the potentially unstable enone intermediate.

(iii) It is possible that substituents could be introduced at C4 of dioxin **206**. This would allow investigation of the influence of dienophilic substituents on the IMDA reaction.

Accordingly, attention was turned to the preparation of iodo-dioxin **207** and its C4-*gem*-dimethyl derivative **208**.

207 **208**

Figure 3.4: *Iodoethyl-dioxins sought for Negishi cross-coupling with c-DHC **190**.*

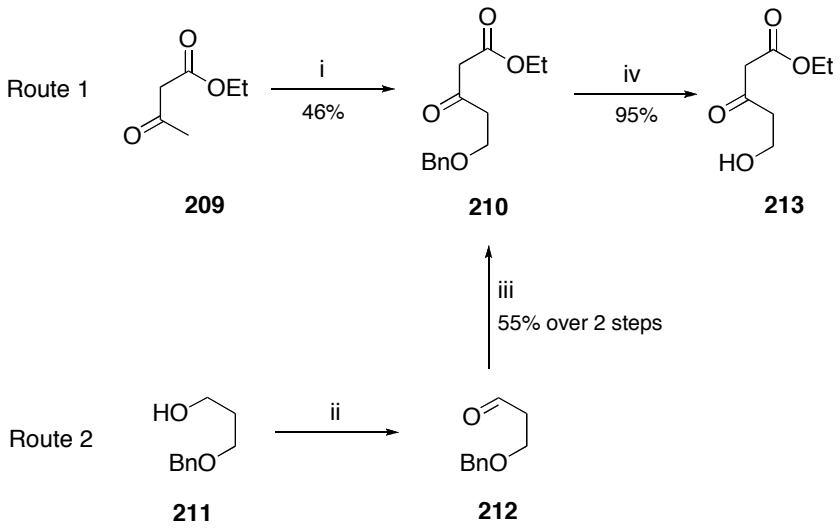
3.3.4 Synthesis of dioxins 207 and 208

3.3.4.1 Unsubstituted iodoethyl-dioxin 207

Iodo-dioxin **207** was prepared *via* the synthetic sequence reported by Funk and co-workers.[127] It was found that some of the reported procedures had to be modified in order to attain the reported yields. These modifications are now discussed, albeit briefly. The synthesis began with the preparation of keto-alcohol **213**, which was achieved *via* two distinct routes (Scheme 3.12). Thus, the procedure of Taylor and LaMattina[129] (Route 1) involves formation of the dianion of ethyl acetoacetate (**209**) and subsequent alkylation with benzyloxymethyl chloride (BOM-Cl) to afford compound **210** in 46% yield. Route 2 followed the protocols of Heathcock *et al*.,[130] and utilised commercially available 3-(benzyloxy)-1-propanol (**211**) as the starting material. This was oxidised, under Swern-Moffit conditions, to the corresponding aldehyde **212**. Treatment of the crude samples of aldehyde **212** with ethyl diazoacetate in the presence of tin (II) chloride furnished β-keto-ester **210** in 55% yield over the two steps. Although there was little difference observed in the overall yield of compound **210** (*ca.* 50%) *via* either route, Route 2 afforded a cleaner reaction that allowed for more ready purification of the product. Accordingly, this second route was preferred. Hydrogenolysis of the benzyl moiety within compound **210** (obtained by either route) was achieved using catalytic $Pd(OH)_2$ to afford keto-alcohol **213** in

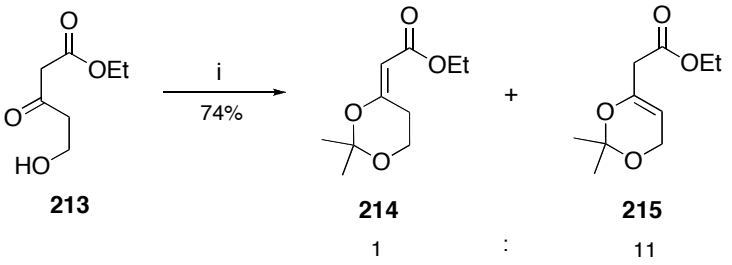
Ω Funk and co-workers have carried out a similar 'one-pot' cycloreversion process followed *in situ* by a cycloaddition reaction on a substrate possessing an amidodioxin moiety.[128]

95% yield. All spectral data collected on this compound were consistent with those reported in the literature.[129]



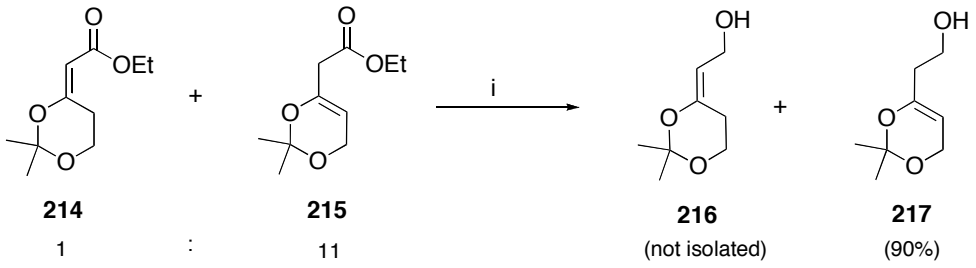
Scheme 3.12: *Reagents and conditions* (i) a) NaH (1.1 mole equiv.), *n*-BuLi (1.05 mole equiv.), THF, -5 °C, 20 min; b) BOM-Cl (1.5 mole equiv.), THF, 0 ºC, 2 h; (ii) oxalyl chloride (1.5 mole equiv.), DMSO (2.0 mole equiv.), CH_2Cl_2, -78 °C, 45 min; (iii) $SnCl_2$ (0.2 mole equiv.), ethyl diazoacetate (1.05 mole equiv.), CH_2Cl_2, 18 °C, 16 h; (iv) $Pd(OH)_2$ on C, H_2 (1 atm), EtOH, 18 ºC, 22 h.

The next stage of the synthesis involved formation of the 1,3-dioxin moiety *via* acid-catalysed protection of alcohol **213** with 2-methoxypropene (Scheme 3.13). Funk and co-workers[127] reported that they observed initial, rapid, formation (1-2 h) of conjugated acetonide **214**, which, after 16 h, had converted, almost exclusively, into the desired endocyclic isomer **215**. In our hands, however, extended reaction times (3 days) were required in order to obtain a satisfactory ratio of compounds **214** and **215** (1:11 as juged by ^{1}H NMR analysis of the crude reaction mixture). The peaks assigned to the major isomer in ^{1}H NMR spectrum are consistent with those reported in the literature for compound **215**.[127]



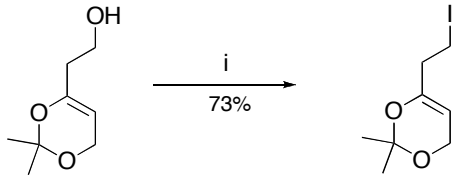
Scheme 3.13: *Reagents and conditions* (i) 2-methoxypropene (3.0 mole equiv.), PPTS (0.3 mole equiv.), THF, 0 to 18 °C, 3 days.

Unfortunately, these isomers were not able to be separated by standard chromatographic methods. As a result, the mixture was treated with lithium aluminium hydride ($LiAlH_4$) to afford the corresponding mixture of alcohols, **216** and **217** (Scheme 3.14). The isomeric alcohols, so formed, could then be separated by column chromatography.



Scheme 3.14: *Reagents and conditions* (i) $LiAlH_4$ (1.5 mole equiv.), Et_2O, 0 °C, 30 min.

The final step in the synthesis of iodo-dioxin **207** involved conversion of alcohol **217** into the corresponding iodide (Scheme 3.15). Following the protocols of Funk and co-workers (PPh_3, I_2, imidazole) the reaction proceeded smoothly to yield (before purification) a mixture of iodide **207** and PPh_3/PPh_3O. Unfortunately, in our hands, iodide **207** proved unstable to column chromatography so it could not be obtained in a pure form. This problem was overcome by employing polymer-bound PPh_3, which allowed pure samples of iodo-dioxin **207** to be obtained in 73% yield.



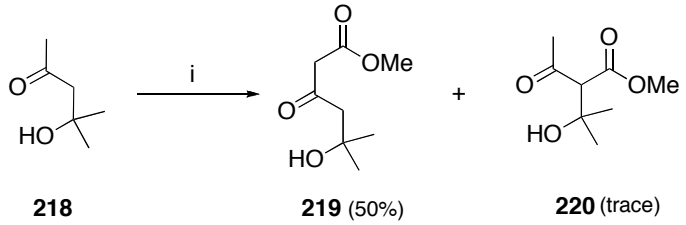
217 **207**

Scheme 3.15: *Reagents and conditions* (i) imidazole (2.3 mole equiv.), polymer-bound PPh_3 (2.0 mole equiv.), I_2 (2 mole equiv.), THF, 0 to 18 °C, 1 h.

Although iodoethyl-dioxin **207** is relatively stable in solution, neat samples were found to rapidly decompose with accompanying loss of molecular iodine. Thus, this compound was stored as its alcohol precursor (**217**) and only converted into the iodide (following the procedure outline above) immediately prior to use.

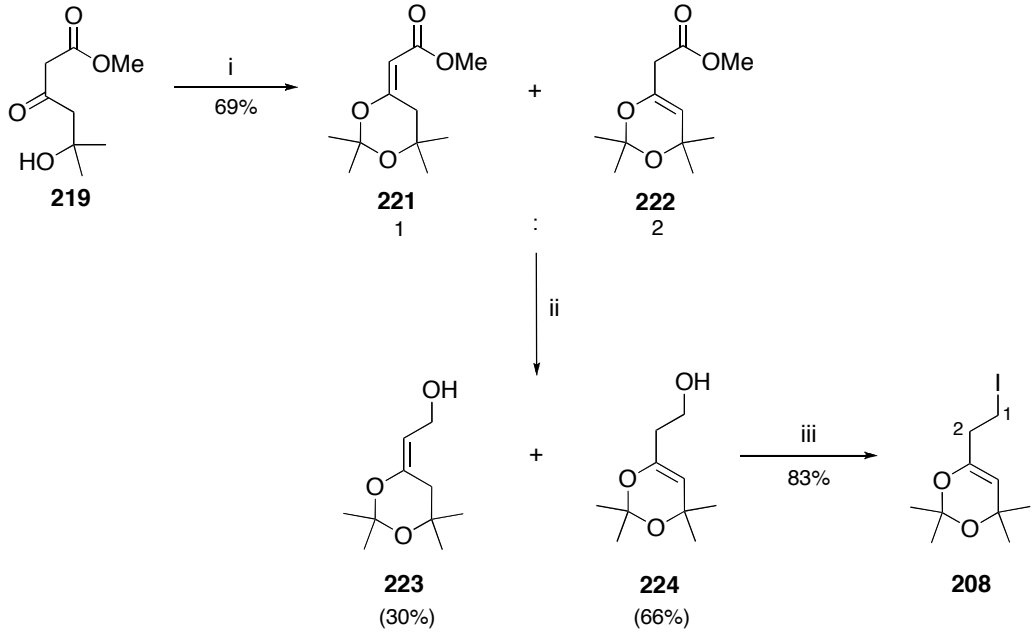
3.3.4.2 C4-*gem*-dimethyl iodo-dioxin 208

With a successful synthesis of iodo-dioxin **207** in hand, attention was turned to the preparation of the C4-*gem*-dimethyl derivative. To this end, disubstituted β-keto-ester **219** was prepared from commercially available 4-hydroxy-4-methyl-2-pentanone (**218**) (Scheme 3.16). β-Hydroxy ketones such as **218** can be doubly deprotonated with two equivalents of an amide base to generate either the proximal or the distal dianions. The enolization and trapping of such systems have been studied by Albizati *et al*.[131] In this work, conditions for regioselective generation of either the proximal or the distal dianion were identified. Accordingly, β-hydroxy ketone **218** was treated with two equivalents of LDA at -78 ºC, then allowed to warm to 18 ºC and stirred for 15 min at this temperature in order to generate the desired distal dianion. Mander's reagent then was added to the resulting solution (at -78 ºC) to afford the desired β-keto-ester **219** in 50% yield. This product was accompanied by traces of compound **220**, formed *via* acylation of the proximal enolate. All spectral data collected on compound **219** were consistent with those reported in the literature.[132]



Scheme 3.16: *Reagents and conditions* (i) a) LDA (2.3 mole equiv.), THF, -78 to 18 °C, 30 min; b) $NCCO_2Me$ (1.05 mole equiv.), THF, -78 °C, 15 min.

Following the modified procedures described in the previous Section (3.3.4.1), β-keto-ester **219** was successfully converted into iodide **208** (Scheme 3.17). Thus, treatment of compound **219** with 2-methoxypropene and pyridinium tosylate (PPTS) afforded, after 3 days, a 1:2 mixture of acetonides **221** and **222**. Various attempts to improve on this ratio proved fruitless. Reduction of the mixture was achieved using $LiAlH_4$ to afford, after chromatographic separation, alcohols **223** and **224**. Finally, alcohol **224** was converted, by standard means, into iodide **208**, which was obtained in 83% yield.

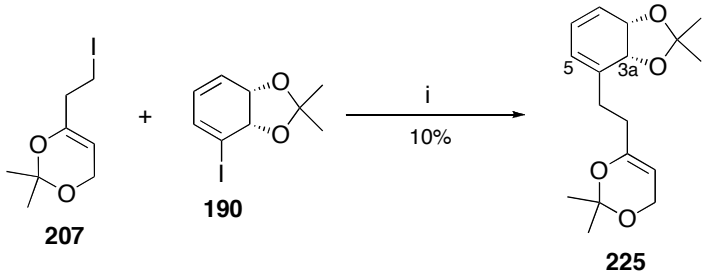


Scheme 3.17: *Reagents and conditions* (i) 2-methoxypropene (3.15 mole equiv.), PPTS (0.3 mole equiv.), THF, 0 to 18 °C, 3 days; (ii) $LiAlH_4$ (1.3 mole equiv.), Et_2O, 0 °C, 30 min; (iii) imidazole (2.5 mole equiv.), polymer-bound PPh_3 (2.0 mole equiv.), I_2 (2.0 mole equiv.), THF, 0 to 18 °C, 1 h.

The ^{1}H NMR spectrum obtained on iodide **208** was fully consistent with the assigned structure. It features a one-proton singlet in the olefinic region along with two two-proton triplets at δ 3.26 and 2.55, which were assigned to the C1 and C2 methylene units, respectively. Two singlets integrating for six protons each confirmed the presence of the two non-equivalent *gem*-dimethyl units. The ^{13}C NMR spectrum provided evidence that the desired iodide substitution had occurred at C1, by virtue of a new signal appearing at δ 2.48, which was attributed to the iodomethylene carbon. Iodide **208** was found to be equally as unstable as its unsubstituted counterpart **207**. Thus, alcohol **224** was also only converted into the iodide **208** immediately prior to use.

3.3.5 Negishi cross-couplings of *cis*-1,2-dihydrocatechols and iodo-dioxins 207 and 208

With the relevant coupling partners in hand, their suitability as participants in Negishi cross-coupling reactions was investigated. To this end, iodide **207** was treated with *tert*-butyllithium at -78 ºC to effect lithium-for-halogen exchange. The resultant anion was then treated with a THF solution of anhydrous $ZnCl_2$ to generate, after warming to 18 ºC, the desired organozinc species. Subsequent addition of a mixture of iodide **190** and catalytic quantities of $Pd(PPh_3)_4$ afforded compound **225**, albeit it in only 10% yield (Scheme 3.18).



Scheme 3.18: *Reagents and conditions* (i) a) *t*-BuLi (3.0 mole equiv.), THF, -78 °C, 15 min; b) $ZnCl_2$ (1.1 mole equiv.), THF, -78 to 18 °C, 30 min; c) **190** (1 mole equiv.), $Pd(PPh_3)_4$ (10 mol%), THF, 18 ºC, 2 h.

The ^{1}H NMR spectrum of triene **225** features signals associated with both the *c*-DHC and the ethyl-dioxin moieties, and was fully consistent with the notion that there had been a successful union of the two coupling partners. The doublets observed at δ 5.73 and 4.55, which can be assigned to C5 and C3a respectively, are characteristic of a coupled product (as described in Section 3.3.2), as are the multiplets at δ 2.41 and 2.26, which can be attributed to the allylic

methylene units of the newly introduced ethyl-dixoin moiety. The ^{13}C NMR spectrum (Figure 3.5) displays the expected seventeen carbon resonances and is fully consistent with the assigned structure. The EI mass spectrum displays a molecular ion at *m/z* 292 and an accurate mass measurement on this species established that it was of the expected molecular composition, *viz*. $C_{17}H_{24}O_4$.

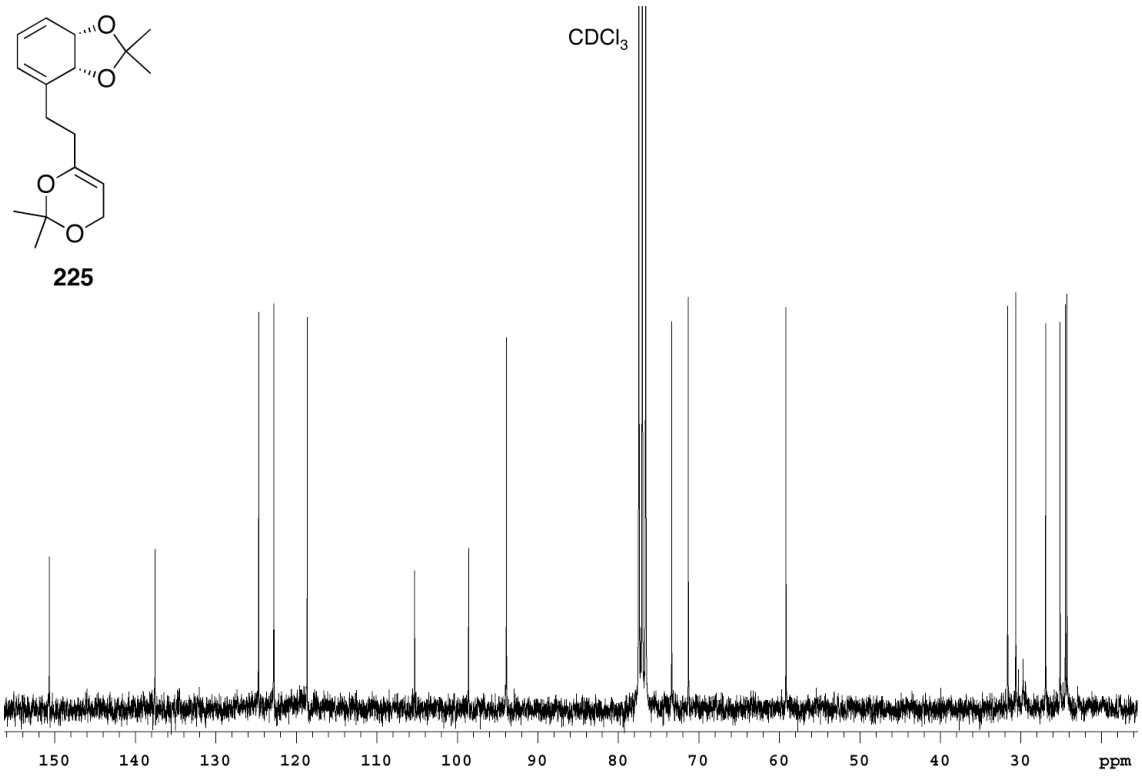
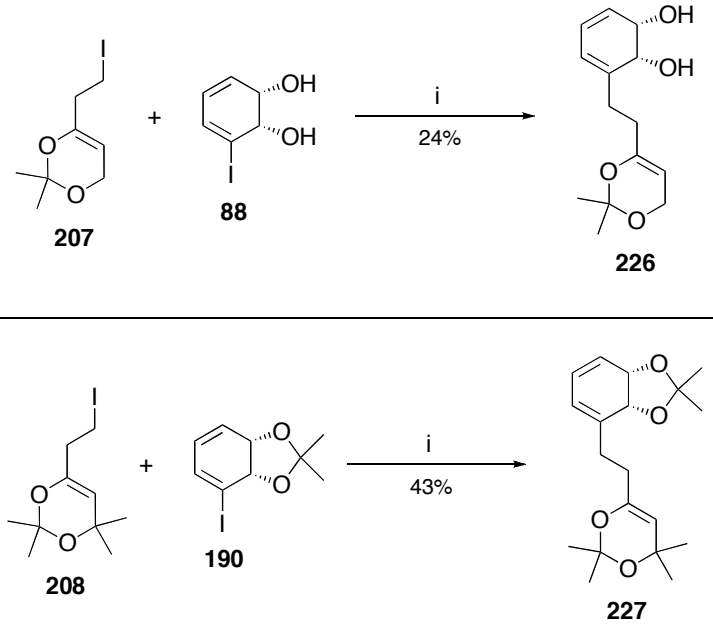


Figure 3.5: *75 MHz ^{13}C NMR spectrum of coupled product **225** (recorded in $CDCl_3$).*

Having successfully coupled compounds **207** and **190**, attention was turned to optimising this process. Unfortunately, and despite extensive efforts, the yield could not be improved beyond *ca.* 30% (which was obtained using 1.5 equivalents of the organozinc coupling partner that had been made using a freshly prepared THF solution of anhydrous zinc chloride).[#] This reaction was also carried out using unprotected *c*-DHC **88** and the C4-*gem*-dimethyl dioxin **208** (Scheme 3.19) to afford compounds **226** (24%) and **227** (43%), respectively. Thus, three different IMDA precursors were able to be synthesised using this type of reaction, albeit only in modest yield.

The reader will observe, in Chapter Four that, for related system significant improvements in yield were observed by replacing $ZnCl_2$ with ZnI_2. However, due to time restraints the reaction described here was not attempted using these improved reaction conditions.



Scheme 3.19: *Reagents and conditions* (i) a) iodo-dioxin partner (1.5 mole equiv.) *t*-BuLi (3.3 mole equiv.), THF, -78 °C, 15 min; b) $ZnCl_2$ (1.65 mole equiv.), THF, -78 to 18 °C, 30 min; c) *cis*-dihydrocatechol partner (1.0 mole equiv.), $Pd(PPh_3)_4$ (10 mol%), THF, 18 ºC, 2 h.

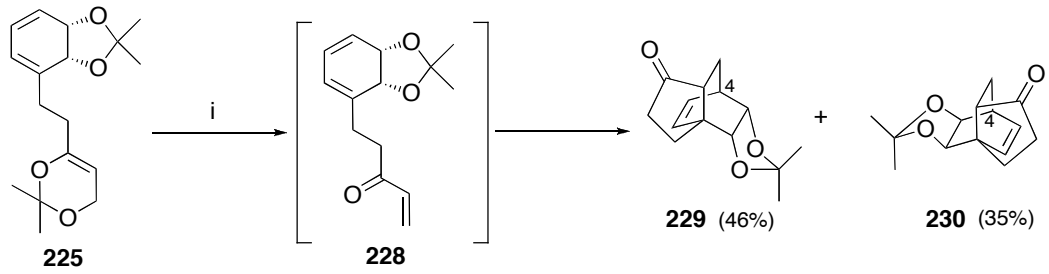
Although none of the desired materials could be obtained in high yield, sufficient quantities of compounds **225, 226** and **227** were available to permit a preliminary assessment of the capacity of these *c*-DHC derivatives to participate in IMDA cycloaddition reactions. The results of such investigations are discussed in the following Section.

3.4 Stereochemical Outcomes of IMDA Cycloaddition Reactions of *cis*-1,2-Dihydrocatechol-Dioxin Conjugates

While *inter*molecular Diels-Alder reactions have a strong preference for an *endo*-transition state, this effect does not dominate the *intra*molecular variant to the same extent.[19] For this reason, there were four possible cycloadducts that could be produced during the reactions under investigation; namely, the i) *endo*-, *anti*- ii) *endo*-, *syn*- iii) *exo*-, *anti*- and/or iv) *exo*-, *syn*-adducts. The aim of the work outlined in the present Section was to investigate the stereochemical outcomes of the *intra*molecular Diels-Alder reactions of *c*-DHC derivatives.

3.4.1 IMDA cycloaddition reaction of precursor 225

Following the procedure of Funk and co-workers,[128] dioxin **225** was heated in refluxing toluene for 16 h in the presence of butylated hydroxytoluene (BHT) (to prevent decomposition *via* autooxidation) and a mild acid scavenger (*N,N*-diethylaniline). Under such conditions, retrocycloaddition of the dioxin moiety was followed by an *in situ* intramolecular Diels-Alder cycloaddition reaction to afford a *ca.* 1:1 mixture of just two (of the possible four) cycloadducts. These were obtained in 81% combined yield and readily separated by column chromatography. Using X-ray crystallography, these compounds were assigned as the *endo*-, *anti*-adduct **225**$^{\Psi}$ and the *endo*-, *syn*-adduct **226*** (Scheme 3.20 and Figure 3.8).



Scheme 3.20: *Reagents and conditions* (i) BHT (0.5 mole equiv.), *N,N*-diethylaniline (14.3 mole equiv.), toluene, reflux, 16 h.

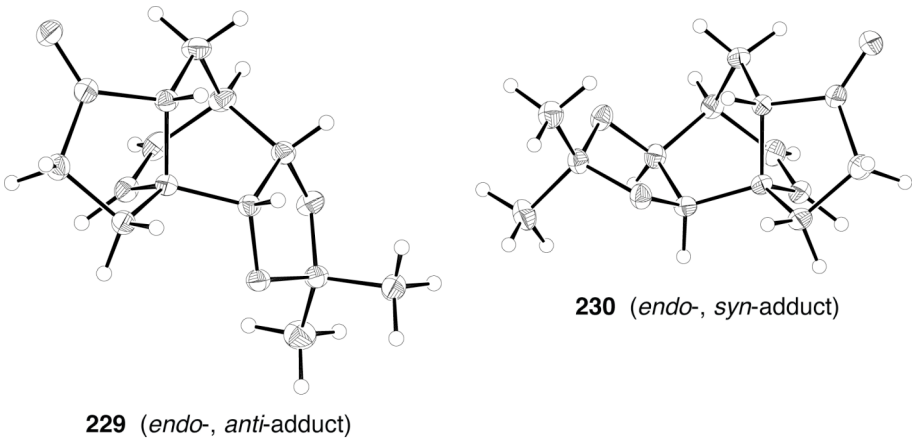


Figure 3.8*: Displacement Ellipsoid Plots (30%) derived from single-crystal X-ray analysis of IMDA adducts* ***229*** *and* ***230*** *(Appendices 9 and 10 respectively).*

Ψ Addition of the dienophile to the face of the diene opposite the acetonide residue.

✶ Addition of the dienophile to the face of the diene bearing the C-O bonds of the acetonide ring.

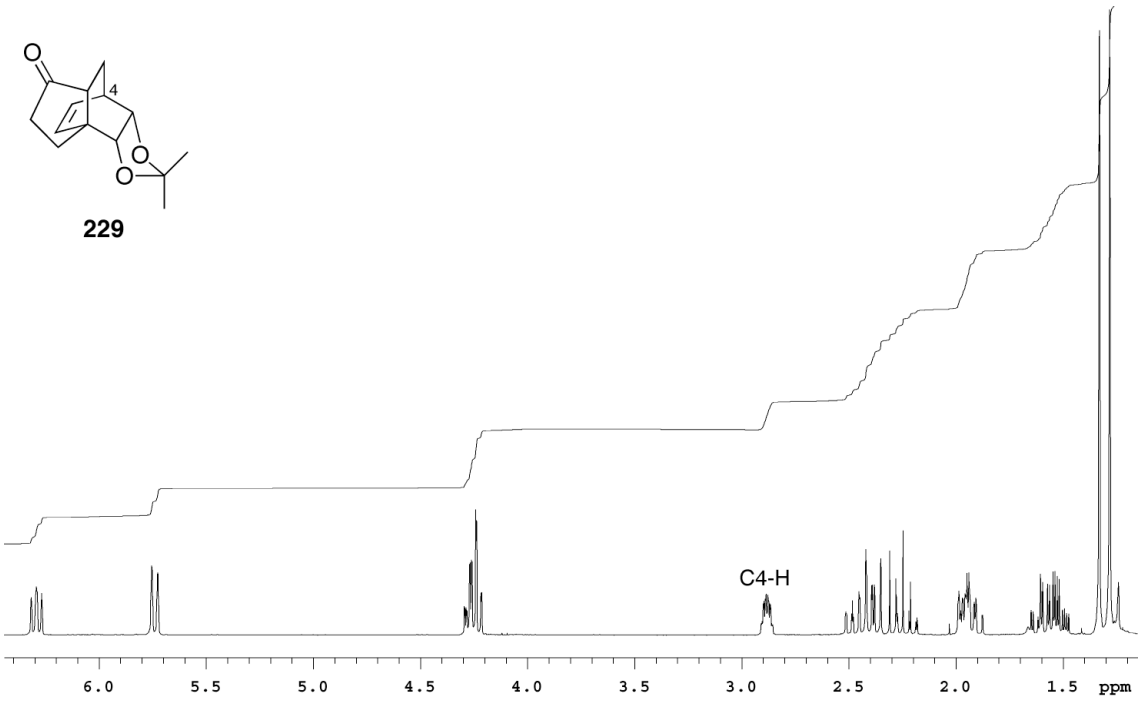


Figure 3.6: *300 MHz ^{1}H NMR spectrum of Diels-Alder adduct **229** (recorded in $CDCl_3$).*

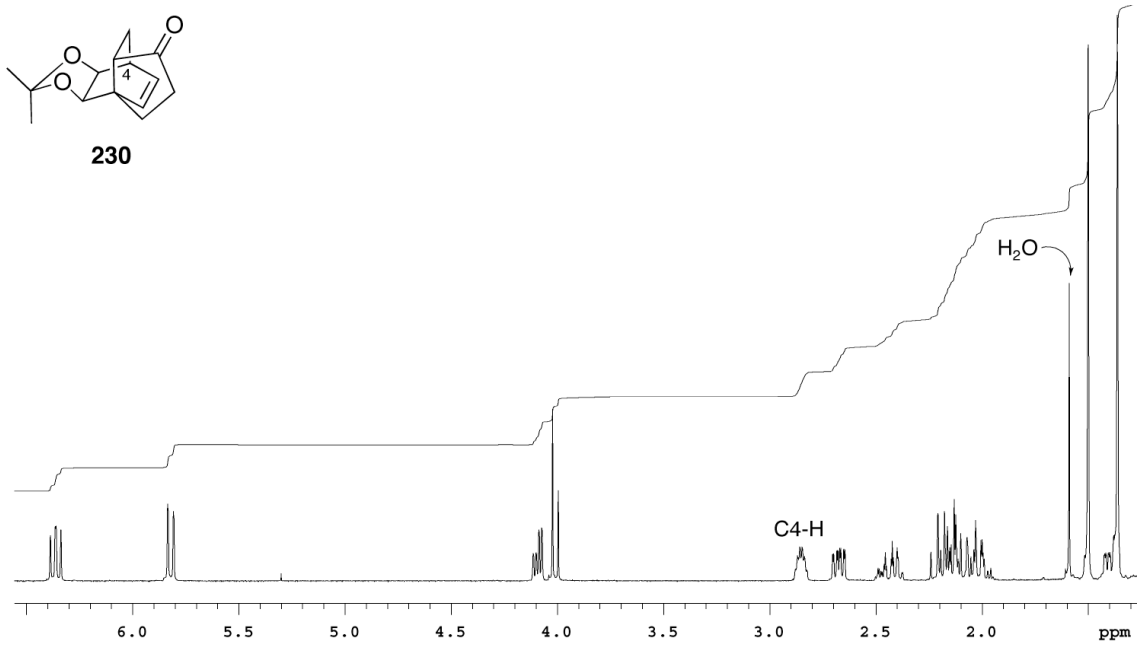


Figure 3.7: *300 MHz ^{1}H NMR spectrum of Diels-Alder adduct **230** (recorded in $CDCl_3$).*

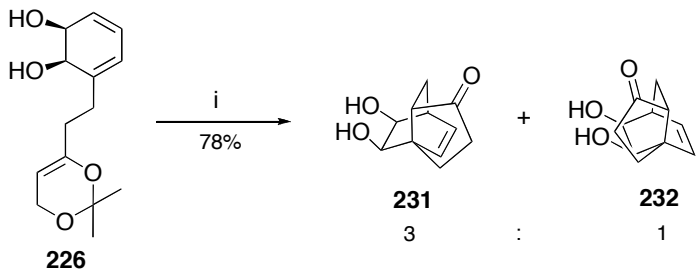
Unsurprisingly, the spectroscopic data obtained on the two adducts were very similar and fully consistent with the assigned structures. Each isomer gives rise to a peak at *ca.* δ 2.8 in the ^{1}H NMR spectrum (Figures 3.6 and 3.7) and this is attributed to a single allylic proton (C4-H). The resonances observed in the olefinic region also display coupling patterns that are characteristic of Diels-Alder adducts of *c*-DHCs[Σ]. Each isomer exhibited a carbonyl stretching band at *ca.* 1740 cm^{-1} in the IR spectrum as is characteristic of a five-membered ring ketone. The molecular formula of each adduct ($C_{14}H_{18}O_3$) was readily established using a combination of mass spectrometry and elemental analysis. Conversely, the melting points of the two isomers were found to be significantly different; melting was observed in the range of 93 - 96 ºC for the *syn*-adduct (**230**) and 131 - 135 ºC for the *anti*-adduct (**229**).

The stereochemical outcome observed for this reaction was unexpected for several reasons. While the *endo*/*exo* selectivity of the cycloaddition reaction could not have been predicted, it was anticipated that the *syn*/*anti* selectivity would follow from the outcomes observed in the analogous intermolecular cycloaddition reactions[26] and thus give the *anti*-adduct as the major product of the reaction. However, it was observed that the cycloaddition occurred stereoselectively, *via* an *endo*-transition state, but with essentially no facial selectivity, affording the *syn*- and *anti*- adducts in a 1:1.1 ratio, respectively. As discussed in Chapter 1, it is widely recognised that both steric and electronic factors contribute significantly to the facial selectivity of Diels-Alder reactions of *c*-DHCs. It has been shown that, in the absence of any pronounced steric effects, stereoelectronic control of the reaction results in preferential formation of the *syn*-adduct. However, by protection of the diol moiety, and the associated increase in bulk, steric interactions become the governing factor, thereby affording the *anti*-adduct as the major product. In the *inter*molecular variant, the acetonide-protecting group was found to provide sufficient steric bulk to override the underlying electronic factors and so leading to the *anti*-adduct as the major product of the reaction. In the *intra*molecular reaction, however, the acetonide-protecting group is clearly not large enough to control the facial selectivity, resulting in a *ca*. 1:1 mixture of *syn*- and *anti*-adducts. Of course, it is possible that the use of a bulkier protecting group could improve the *anti*-selectivity of this reaction.[24]

Σ See Chapter Two, Section 2.3.1 for a description of characteristic resonances observed in the ^{1}H NMR spectra of Diels-Alder adducts of *cis*-1,2-dihydrocatechols.

3.4.2 IMDA cycloaddition reaction of precursor 226

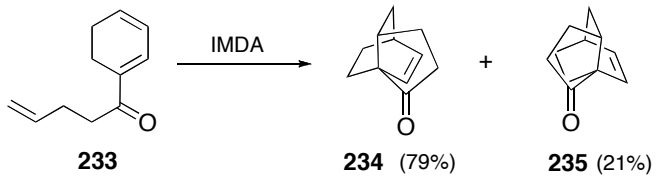
On heating under the same conditions as described in the preceding Section (3.3.6.1), diol **226** underwent a retrocycloaddition then an IMDA cycloaddition reaction to afford a 3:1 mixture of two cycloadducts in 78% combined yield. There were several indications that the stereochemical outcome of this cycloaddition reaction was different to that observed for the previous one. For example, the olefinic resonances in the ^{1}H NMR spectrum were notably different for the two isomers, a feature not usually observed for mixtures of *syn*- and *anti*-adducts. It was, therefore, proposed that this reaction had occurred with excellent facial selectivity, most probably delivering the *syn*-adduct preferentially, but with only moderate stereoselectivity to give a mixture of the *syn*-, *endo*- (**231**) and *syn*-, *exo*- (**232**) cycloadducts (Scheme 3.21).



Scheme 3.21: *Reagents and conditions* (i) BHT (0.1 mole equiv.), *N,N*-diethylaniline (8.0 mole equiv.), toluene, reflux, 16 h.

Owing to the small scale of the reaction and the difficulties associated with chromatographic separation of these isomers, it was not possible to confirm this tentative assignment by X-ray crystallography. Thus, it was necessary to confirm the stereochemistry of the two cycloadducts by other means, namely by NMR and chemical correlation techniques. The ^{1}H NMR spectrum of the mixture (Figure 3.10) clearly exhibits two quite distinct sets of olefinic resonances in a 3:1 ratio. The major product gives rise to peaks in the olefinic region at δ 6.32 (dd, J = 8.2 and 6.6 Hz) and 5.83 (d, J = 8.2 Hz) and an essentially reversed pattern is displayed by the minor component with resonances observed at δ 6.23 (d, J = 8.2 Hz) and 6.13 (dd, J = 8.2 and 6.3 Hz). Krantz and co-workers have reported a remarkably similar pattern of reciprocity between the olefinic resonances of a related set of *endo*- and *exo*-isomers.[133] In their example, triene **233** undergoes an IMDA cycloaddition reaction to yield isomeric tricyclic ketones **234** and **235** in 79% and 21% yields, respectively (Scheme 3.22). The NMR spectra of these two cycloadducts are shown in Figure 3.9. Notably, the shifts for the two vinyl hydrogens are larger for the

endo-isomer than the *exo*-isomer and the coupling pattern is reversed. This compares favourably with the pattern observed in the ^{1}H NMR spectrum of the mixture of cycloadducts **234** and **235**, thereby lending support to the proposition that a mixture of *endo*- and *exo*-adducts was obtained in which the former isomer was the major one.



233 **234** (79%) **235** (21%)

Scheme 3.22: *Intramolecular Diels-Alder reaction of triene **233** to afford a mixture of* endo- *(**230**) and* exo- *(**231**) cycloadducts.*[133]

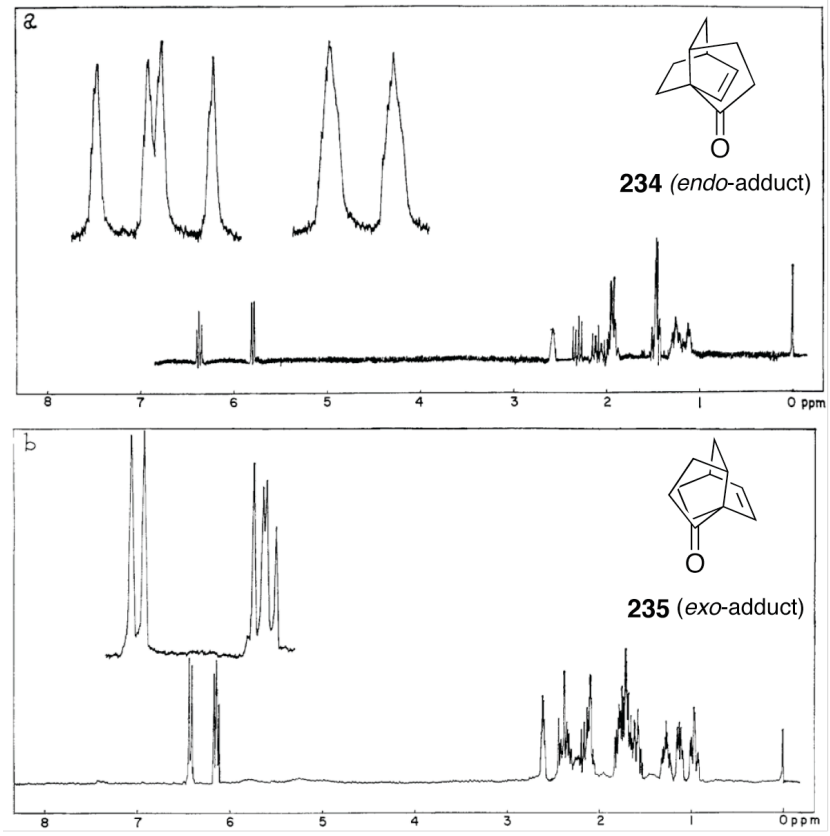


Figure 3.9: *300 MHz ^{1}H NMR spectra of Diels-Alder adducts **234** and **235** (recorded in $CDCl_3$ by Krantz and co-workers).*[133] *Reprinted with permission from* J. Am. Chem. Soc.*, 95, 5662. Copyright (1973) American Chemical Society.*

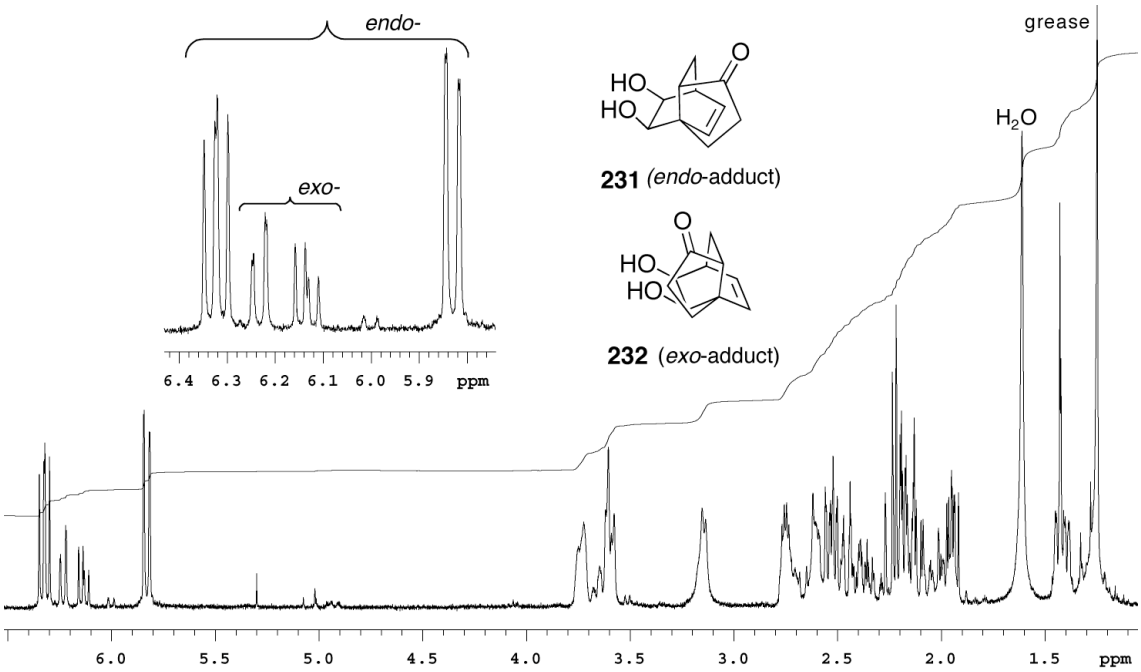


Figure 3.10: *300 MHz ^{1}H NMR spectrum of the products of the IMDA cycloaddition reaction of triene* ***226*** *(recorded in $CDCl_3$).*

With assignment of one aspect of the stereochemistry achieved, the facial selectivity of the reaction required investigation, particularly because it was evident from the IMDA cycloaddition reaction with precursor **225** that the facial selectivity cannot be predicted based on the corresponding intermolecular DA cycloaddition reactions. Since the acetonide derivatives of the *endo-, anti-* (**229**) and the *endo-, syn*-cycloadducts (**230**) had already been prepared, and their structures confirmed by X-ray crystallography (Figure 3.6), the diols were converted into the corresponding acetonides to enable assignment of the facial selectivity (Scheme 3.23).

Scheme 3.23: *Reagents and conditions* (i) $(MeO)_2CMe_2$, (15.0 mole equiv.), *p*-TsOH•H_2O (0.4 mole equiv.), CH_2Cl_2, 18 °C, 16 h.

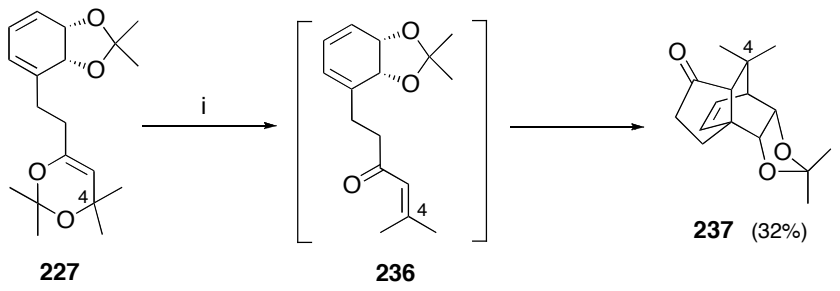
On subjecting the mixture of diols to protection, using standard protocols, as the corresponding acetonide, it was surprising to find that only one product was observed in the ^{1}H NMR spectrum

of the crude reaction mixture. Upon comparing this spectrum with that of cycloadducts **229** and **230** it became evident that the compound that had been obtained was the *syn*-, *endo*-isomer (**230**), thereby establishing that the IMDA cycloaddition reaction was *syn*-selective. The disappearance of the corresponding *syn*-, *exo*-isomer was unexpected and may be due to acid-induced epimerisation. Ouellett and co-workers have previously conducted base-induced epimerisation studies with a number of substituted bicylo[2.2.2]octenes, demonstrating that under equilibration conditions there is a preference for the *endo*-substituted congener.[134] This was proposed, by the authors, to be a consequence of unfavourable steric interactions in the *exo*-adducts. Studies to determine if cycloadducts **231** and **232** demonstrate similar behaviour are now underway.

In summary, it has been established that the IMDA cycloaddition reaction of the unprotected *c*-DHC derivative **226** occurred with excellent facial selectivity, affording only the *syn*-adduct. However, unlike previous examples of DA cycloaddition reactions, only moderate diastereoselectivity was obtained, affording a mixture of *endo*- and *exo*-isomers in a 3:1 ratio, respectively.

3.4.3 IMDA cycloaddition reaction of precursor 227

The IMDA cycloaddition reaction of the bis-*gem*-dimethylated system **227** was the last to be studied. Under the same reaction conditions as described previously (toluene, *ca.* 110 ºC, 16 h), no reaction was observed. However, on changing the solvent from toluene to mesitylene and heating the reaction mixture at 165 ºC for 4 days, two reaction products were observed. Unfortunately, there was also a substantial amount of dioxin **227** remaining (~25% after 4 days), which could not be induced to undergo further reaction by simply increasing the duration of the reaction. ^{1}H NMR analysis of the crude reaction mixture revealed that one products was, as determined by the presence of characteristic olefinic resonances, indeed an IMDA cycloadduct. However, the presence of three distinct olefinic signals associated with the second product was indicative of a dimeric species resulting from a DA reaction between two *c*-DHC moieties. Owing to the small scale of the reaction, the dimer could not be isolated and characterised. However, its presence was confirmed by EI-inducted mass spectroscopy of the crude reaction mixture. The IMDA cycloadduct was eventually isolated in 32% yield (Scheme 3.24) and its structure confirmed by single-crystal X-ray analysis (Figure 3.12, Appendix 12) as the *endo*-, *anti*-isomer **237**.



Scheme 3.24: *Reagents and conditions* (i) BHT (0.1 mole equiv.), *N,N*-diethylaniline (14.1 mole equiv.), mesitylene, reflux, 4 days.

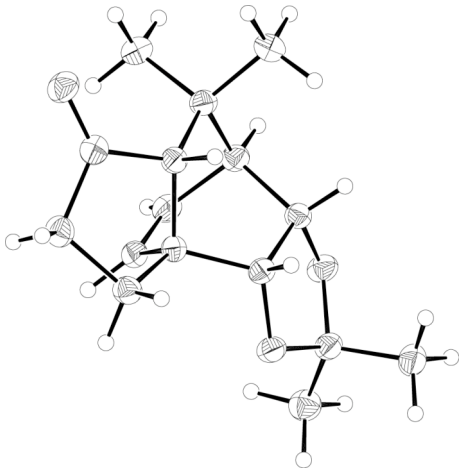


Figure 3.12*: Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of IMDA adduct* ***237****.*

The presence of the *gem*-dimethyl group at C4 of the dioxin moiety appears to have significantly affected both stages of this reaction. Firstly, the observation that significant amounts of the starting dioxin **227** could be re-isolated while none of the corresponding enone **233** was observed suggests that the methyl groups hinder the cycloreversion process. Thus, higher temperatures (165 ºC *cf.* 110 ºC) and longer reaction times are required to overcome the greater activation energy. Secondly, the steric influence of the methyl groups also affected the stereochemistry of the IMDA cycloaddition reaction, with addition of the dienophile occurring solely at the face of the diene opposite to the acetonide residue, and thus affording only the *anti*-adduct. In contrast, the IMDA cycloaddition reaction involving the unsubstituted derivative **225** yielded a *ca.* 1:1 mixture of *syn*- and *anti*-adducts.

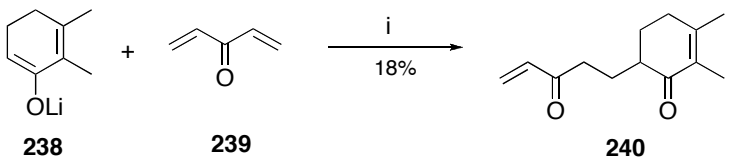
3.4.4 Conclusion

This work was initiated with the aim of investigating IMDA cycloaddition reactions of *c*-DHCs. The data presented here show that these reactions are *syn*-selective for the unprotected *c*-DHC, while protection of the diol moiety with an acetonide results in a mixture of *syn*- and *anti*-adducts. The alteration of the facial selectivity through the use of protecting groups is promising and it is hoped that bulkier protecting groups will further improve the *anti*-selectivity of the process. Additionally, while substitution at C4 of the dioxin improves the *anti*-selectivity of the IMDA reaction it appears to adversely affect the efficiency of the retrocycloaddition reaction of the dioxin moiety. Thus, the development of synthetic routes to substrates for the IMDA reaction that posesses unprotected dienophilic moieties would greatly enhance the versatility of this methodology.

3.5 Synthesis of IMDA Precursors *via* a Conjugate Addition Reaction

3.5.1 Introduction

Owing to the abovementioned problems associated with the previous strategy, the development of an alternative procedure for the synthesis of the IMDA precursors was necessary. A survey of the literature suggested divinyl ketone (DVK) **239** might be a suitable reagent for the introduction of the desired dienophilic moiety.[135,136] While DVK is capable of undergoing a double Michael addition, Spitzner *et al.* found that, under aprotic conditions, it reacts with anions such as **238** to afford the product of a single Michael addition, compound **240**, as the exclusive product of the reaction. (Scheme 3.25).[135] Hagiwara *et al.* subsequently reported improved yields of such products (41 - 49%) *via* addition of HMPA and quenching at low temperature.[136]



238 **239** **240**

Scheme 3.25: *Reagents and conditions* (i) THF, -70 ºC, 15 mins.

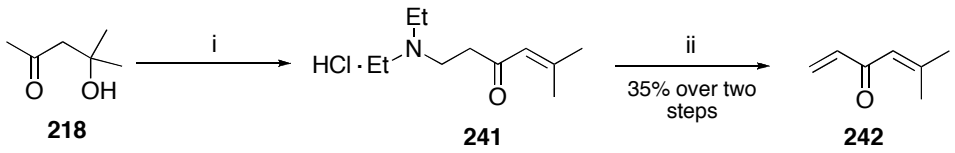
Thus, it was envisioned that conjugate addition of an anion derived from *c*-DHC to DVK would allow the rapid synthesis of the desired IMDA precursors without the need to protect the

α,β-unsaturated ketone moiety. Furthermore, if substituted derivatives of DVK are used in this reaction it was expected that the conjugate addition process would occur at the less sterically hindered end, yielding IMDA precursors incorporating substituted dienophilic residues. The following Section details the synthesis of DVK (**239**) and its *β,β*-dimethylated derivative **242**.

3.5.2 Synthesis of divinyl ketones

Despite the many reported uses of DVK in the literature,[137] acquiring sufficient quantities of this reagent proved to be surprisingly difficult. Specifically, its volatility, propensity to polymerise and lachrymatory properties made the isolation of DVK and its derivatives highly challenging. After several protocols were evaluated, the preparations reported below were found to be the most reliable ones for obtaining useful quantities of DVK and its *β,β*-dimethylated derivative.

The *β,β*-dimethylated DVK **242** was found to be most easily prepared *via* the method of Mironov and co-workers.[138] This involved a Mannich reaction between diacetone alcohol **218**, formaldehyde and diethylamine hydrochloride and subsequent decomposition of the ensuing Mannich base **241** at 150-210 ºC, to afford compound **242**[139] in 35% yield (Scheme 3.26). Although this yield is low, the reagents are inexpensive and the reaction can be readily scaled-up in order to obtain multi-gram quantities of the desired product.

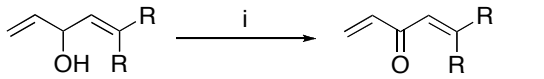


Scheme 3.26: *Reagents and conditions* (i) Et_2NH•HCl (1.0 mole equiv.), CH_2O (1.0 mole equiv.), hydroquinone (0.02 mole equiv.), HCl (trace), 100 ºC, 2h; (ii) 150 – 200 ºC.

While Mironov and co-workers reported that acetone works equally well in this reaction, and thus gives the parent DVK **239**, this process proved difficult to reproduce. Accordingly, an alternative route, involving oxidation of divinyl carbinol **199** to the corresponding ketone **239**, was used.[Δ] After screening various oxidants, DDQ was found to be the most effective, affording

Δ This reaction was modified from the work of Reed and co-workers who oxidised carbinol **199** to DVK **239** in yields of between 5–50% using manganese dioxide.[140]

DVK (**239**)[141] in 72% yield.[θ] It should be noted that the *β,β*-dimethylated DVK **242** can also be made *via* this route (Scheme 3.27); however, the method shown in Scheme 3.26 was routinely used, as it was the less expensive option.



199 R = H
243 R = Me

239 R = H (72%)
242 R = Me (41%)

Scheme 3.27: *Reagents and conditions* (i) DDQ (1.1 mole equiv.), Et_2O, 18 ºC, 24 h.

Since the reaction conditions used are rather mild it is anticipated that this method will be able to be applied in the preparation of more highly functionalised divinyl ketone derivatives for the synthesis of more complex IMDA precursors in future studies.

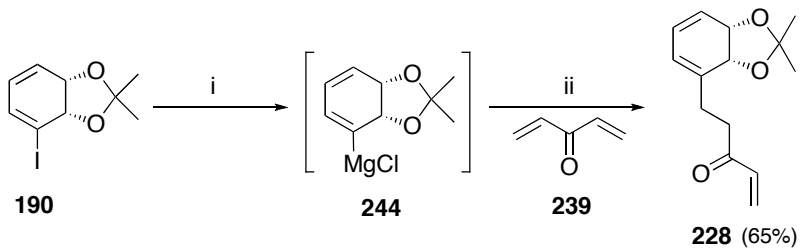
3.5.3 The conjugate addition reaction

With the desired Michael acceptors now in hand, the pivotal conjugate addition reaction could be examined. To this end, the acetonide protected *c*-DHC **190** was treated with *i*-PrMgCl in order to generate the corresponding Grignard reagent **244**. It is recognised that the magnesium-for-halogen exchange of alkenyl iodides is slow and often requires the use of highly reactive magnesium reagents and/or warming to room temperature in order to obtain synthetically useful results.[142-144] Alkenyl iodide **190** proved to be no exception in this regard with the exchange reaction requiring 1-2 h[ϕ] at 0 ºC to achieve full conversion to the magnesium derivative (as determined by ^{1}H NMR of a sample of the reaction mixture). Intermediate **244** was subsequently treated with CuBr•SMe_2 and HMPA, followed by the addition of a mixture of DVK (**239**) and TMSCl.[145,146] Under these conditions, the expected 1,4-addition process took place to afford, following workup,[ℵ] the desired product **228** in 65% yield (Scheme 3.28).

θ The product is obtained as a solution in Et_2O and pentane. Most of the solvent can be removed under reduced pressure although a small amount of product is lost during this process. To minimise loss of product the solution is reduced until it is *ca.* 60% solution in Et_2O/pentane.

ϕ The progress of this conversion was routinely checked by 1H NMR as the times required for the exchange reaction to go to completion were found to vary and it could not be monitored by tlc.

ℵ The initial product of the reaction is the trimethylsilyl enol ether derivative of compound **228**, which is subsequently hydrolysed on workup to afford the product shown. There were instances in which the silyl enol ether was not fully hydrolysed and in these cases the crude product was stirred, for a brief period, with TBAF to complete the conversion.



Scheme 3.28: *Reagents and conditions* (i) *i*-PrMgCl (1.2 mole equiv.), THF, -30 to 0 ºC, 2h; (ii) CuBr•SMe_2 (0.1 mole equiv.), HMPA (3.0 mole equiv.), TMSCl (3.0 mole equiv.), **239** (2.1 mole equiv), THF, -78 to 18 ºC, 16 h.

As expected, the ^{1}H NMR spectrum of α,β-unsaturated ketone **228** (Figure 3.13) features six signals in the olefinic region. The resonances attributed to the alkene of the α,β-unsaturated ketone moiety are distinct from those due to the *c*-DHC subunit and the magnitude of the couplings allowed full assignment of this region of the spectrum (see Figure 3.13 for assignments). Signals corresponding to the oxymethine protons C3a-H and C7a-H were observed at δ 4.66 and 4.53, respectively, while the peaks at δ 2.56 and 2.83 were assigned to the C8 and C9 methylene units. The APT ^{13}C NMR spectrum (Figure 3.14) exhibits the expected fourteen carbon resonances while the EI mass spectrum shows a molecular ion at *m/z* 234. An accurate mass measurement on this species established that it was of the expected elemental composition, *viz.* $C_{14}H_{18}O_3$.

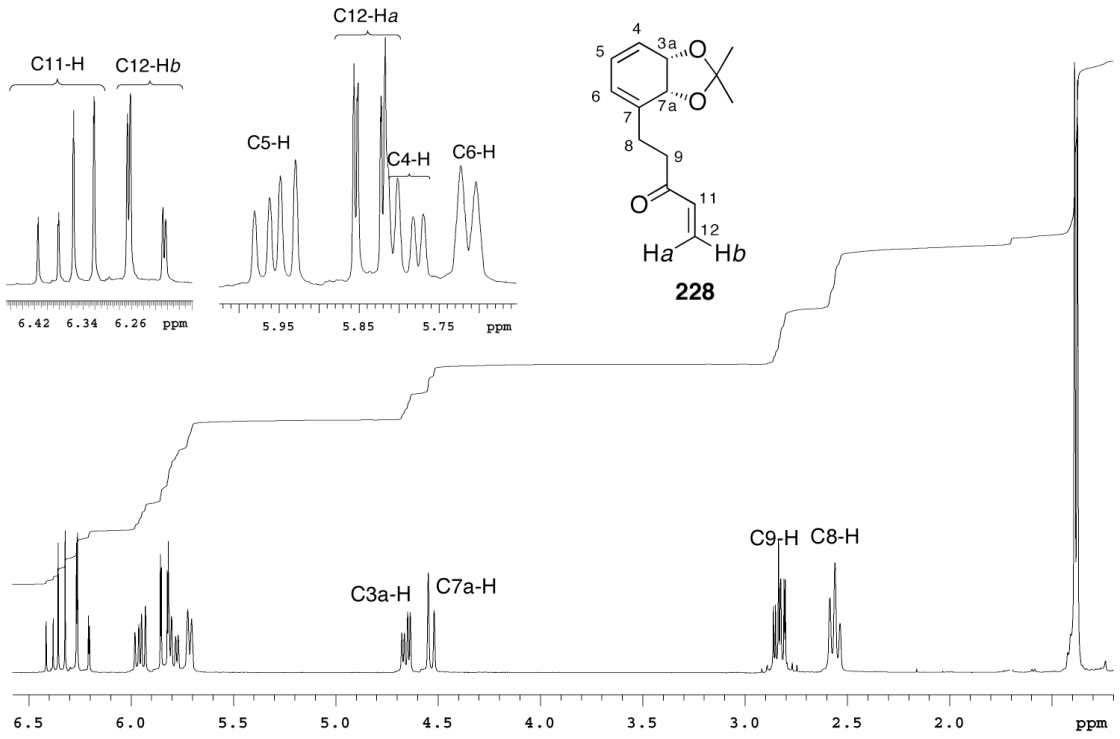


Figure 3.13: *300 MHz ^{1}H NMR spectrum of compound **228** (recorded in $CDCl_3$).*

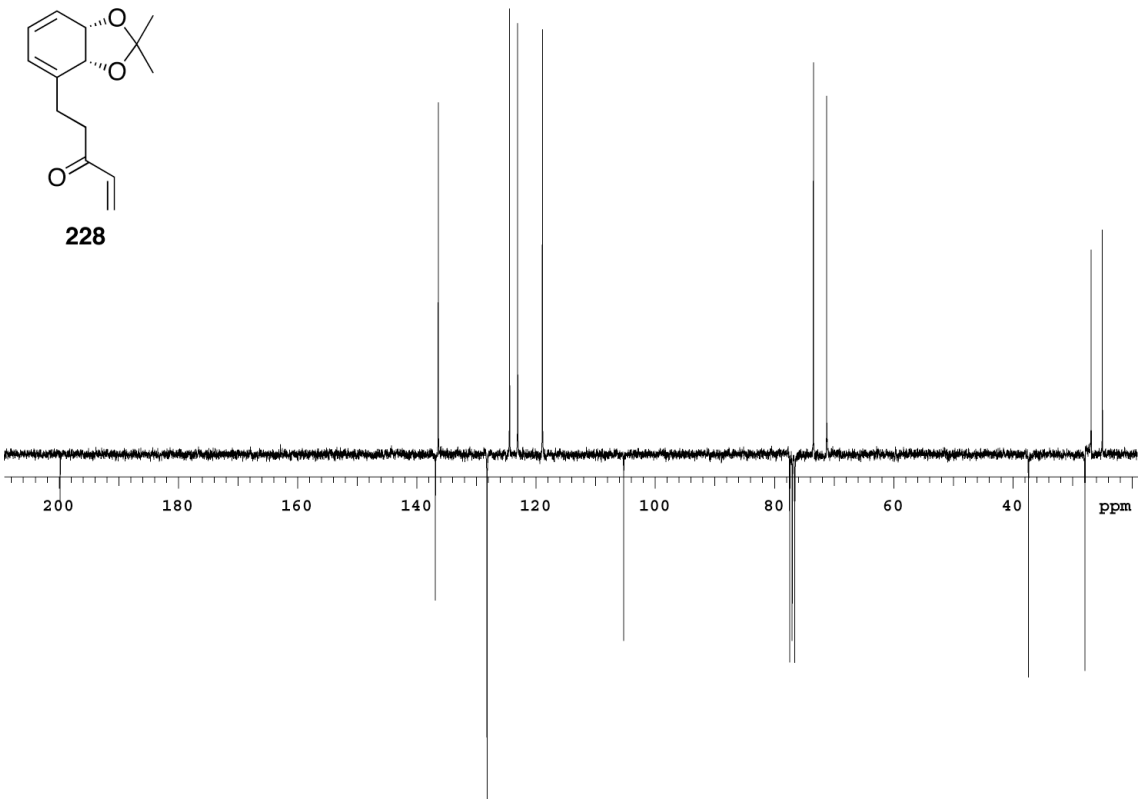


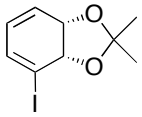
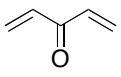
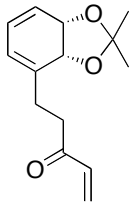
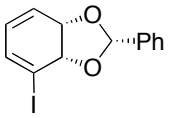
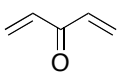
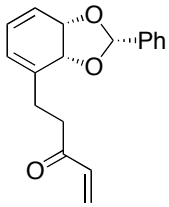
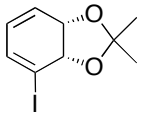
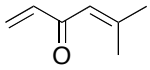
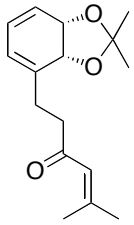
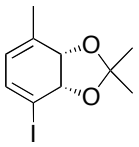
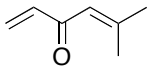
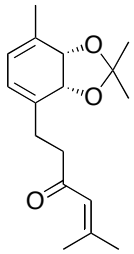
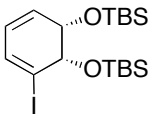
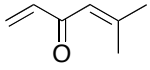
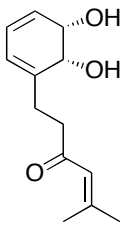
Figure 3.14: *75 MHz APT ^{13}C NMR spectrum of compound **228** (recorded in $CDCl_3$).*

Having identified suitable conditions for the conjugate addition reaction, it remained to synthesise a range of IMDA precursors to allow further investigation into the cycloaddition reactions of these types of *c*-DHC derivatives (Table 3.1). Firstly, and in order to investigate the influence of a bulkier protecting group on the facial selectivity of the IMDA cycloaddition reaction, the *endo*-benzylidene acetal derivative **245** of iodo-diol **88** was prepared using standard procedures.[147] Compound **245** was subsequently engaged in a conjugate addition reaction with DVK (**239**) to afford the desired product, **246**, in 63% yield (Entry 2).

Attention was next directed towards the synthesis of IMDA substrates carrying substituents on the dienophile and/or the diene. Accordingly, acetonides **190** (Entry 2) and **247** (which is substituted at C7 of the diene, Entry 4) were added to *gem*-dimethyl DVK **242**. As anticipated, the conjugate additions occurred exclusively at the less substituted end of the potentially "double" Michael acceptor to afford compounds **236** and **248**, respectively.

Finally, an IMDA precursor with free hydroxy groups was sought. Initial efforts involved cleavage of the acetonide residue of compound **228** or the benzylidene acetal of **246** to reveal the diol moiety. However, despite screening a number of reaction conditions, the desired diol was never obtained. Rather, phenolic by-products were often observed, indicating the major reaction pathway was *via* aromatisation of the *c*-DHC moiety. Consequently, iodo-diol **88** was protected as the bis-(*t*-butyldimethylsilyl) (TBS) ether **249** in the belief that these protecting groups would be able to be removed under milder and non-acidic conditions. Although preparation of the magnesium derivative of bis-TBS ether **249** was unsuccessful, it was found that it could, instead, be converted into the corresponding stoichiometric copper reagent using a procedure described by Noyori *et al*.[148,149] Thus, bis-ether **249** was metallated using *tert*-butyllithium and the resulting lithiospecies was treated with copper (I) iodide (1 mole equivalent) and tributylphosphine (3 mole equivalents) to generate the mixed cuprate. Conjugate addition of this species to DVK **242** and subsequent deprotection of the silyl groups using TBAF afforded diol **250** in 33% yield. An equivalent reaction was also attempted between bis-ether **249** and unsubtituted DVK (**239**) but with no success. Although tlc analysis of the crude reaction suggested that the conjugate addition reaction been successful the Michael product was unstable to the basic deprotection conditions (TBAF) used and rapidly decomposed, possibly *via* polymerisation processes. Due to time restraints these reactions were not pursed any further by the author but studies directed towards optimising this protocol are being continued by other members of the group.

Table 3.1: *Conjugate additions of* c-*DHC derivatives to divinyl ketones* ***239*** *and* ***242****.*

Entry	*cis*-dihydrocatechol derivative	Michael acceptor	product	yield (%)
1⊘	 **190**	 **239**	 **228**	65
2⊘	 **245**	 **239**	 **246**	63
3⊘	 **190**	 **242**	 **236**	74
4⊘	 **247**	 **242**	 **248**	60
5✱	 **249**	 **242**	 **250**	33

⊘*Reagents and conditions:* (i) *i*-PrMgCl (1.2 mole equiv.), THF, -30 to 0 ºC, 2h; (ii) CuBr•SMe_2 (0.1 mole equiv.), HMPA (3.0 mole equiv.), TMSCl (3.0 mole equiv.), **239**/**242** (2.1 mole equiv), THF, -78 to 18 ºC, 16 h.

✱*Reagents and conditions:* (i) *t*-BuLi (2.0 mole equiv.), Et_2O, -78 ºC, 3h; (ii) CuI (1.0 mole equiv.), *n*-Bu_3P (2.5 mole equiv.), THF, -78 ºC, 15 min; (iii) HMPA (3.0 mole equiv.), TMSCl (3.0 mole equiv.), **242** (2.1 mole equiv), THF, -78 to 18 ºC, 16 h; (iv) TBAF, THF, 0 to 18 ºC, 2 h.

The most significant features observed in the ^{1}H NMR spectrum of diol **250** are the resonances associated with the diol moiety (Figure 3.15). The broad doublets at δ 2.45 and 2.93 correspond to the hydroxyl groups and the signals at δ 4.07 and 4.27 are consistent with the presence of oxymethine protons at C3a and C7a respectively. The infrared spectrum of this compound also supports the presence of free hydroxyl groups as judged by the appearance of an OH stretching band at 3372 cm^{-1}.

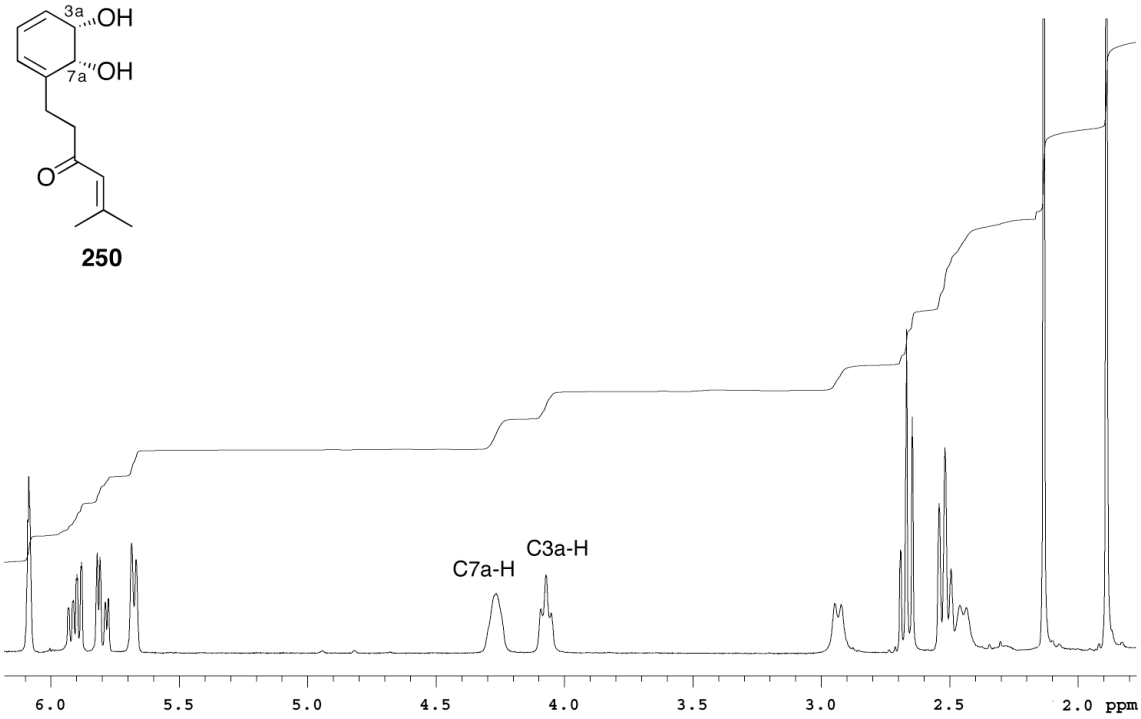
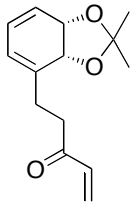
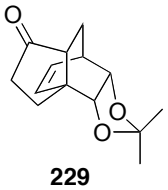
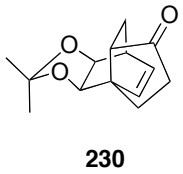
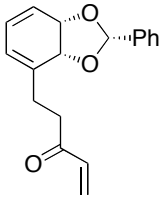
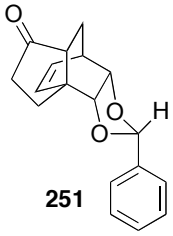
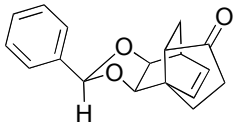
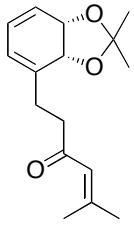
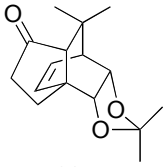
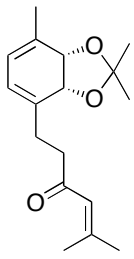


Figure 3.15: *300 MHz ^{1}H NMR spectrum of compound **250** (recorded in $CDCl_3$).*

3.6 Stereochemical Outcomes of IMDA Cycloaddition Reactions of *cis*-1,2-Dihydrocatechol-Enone Conjugates

With five *c*-DHC-based IMDA substrates, **228**, **246**, **236**, **248**, and **250**, in hand (see Table 3.1), the stereochemical outcomes of their IMDA cycloaddition reactions were investigated. The cycloaddition reactions were performed using dilute solutions of the substrates in refluxing toluene (*ca*. 110 ºC) or mesitylene (*ca.* 165 ºC). Catalytic amounts of BHT were added to the reaction mixtures and the product ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. These ratios were found to be essentially the same as those obtained for the isolated and purified products. The results of the IMDA cycloaddition reactions are summarised in Table 3.2.

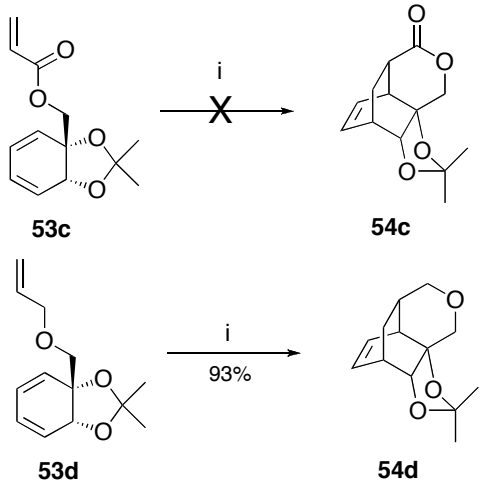
Table 3.2: *IMDA cycloaddition reactions of* c-*DHC derivatives.*

Entry	IMDA substrate	reaction conditions	*anti*-adduct	yield (%)	*syn*-adduct	yield (%)
1	 **228**	toluene, BHT, reflux, 16 h	 **229**	44	 **230**	39
2	 **246**	toluene, BHT, reflux, 16 h	 **251**	59	 **252**	21
3	 **236**	mesitylene, BHT, reflux, 4 days	 **237**	45	Not observed	
4	 **248**	mesitylene, BHT, reflux, 4 days	Observed by ^{1}H NMR but not isolated	<10 %	Not observed	

The IMDA cycloaddition reaction of the acetonide derivative **228** (Entry 1) was found to afford the same ratio of adducts **229** and **230** (1:1.1 respectively) as the cycloaddition reaction of the corresponding dioxin precursor **225** (Section 3.4.1) and these products were obtained in comparable yields. The use of a bulkier protecting group, as demonstrated by the *endo*-benzylidene acetal derivative **246** (Entry 2), was found to increase the selectivity for the *anti*-adduct affording a *ca.* 3:1 mixture of adducts **251** and **252**, respectively. Once again, higher temperatures and longer reaction times were required to ensure complete consumption of precursor **236** which possesses a substituted dienophile (Entry 3). No reaction of this substrate was observed when toluene was used as the solvent. There are two explanations for the lower yield of this reaction than the ones involving precursors **228** and **246**. Firstly, despite extended

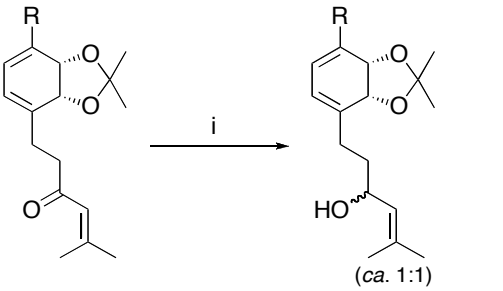
reaction times (up to 7 days), the cycloaddition process never proceeded to completion. Secondly, despite using very dilute solutions (0.005 M), dimerisation, *via* intermolecular cycloaddition of the DHC moiety, was observed. These difficulties were even more pronounced for precursor **248** (Entry 4), which is substituted on both the diene and dienophile. ^{1}H NMR analysis of the crude reaction mixture revealed it was composed primarily of precursor **248** and its Diels-Alder dimer, with only small amounts of IMDA product present (<10%). Finally, the IMDA cycloaddition reaction of diol **250** (not featured in Table 3.2) was unsuccessful. No reaction was observed on heating this substrate refluxing in toluene, due to the substitution on the dienophile, while temperatures higher than *ca.* 110 ºC were found to cause aromatisation of the *c*-DHC moiety. Although this result was disappointing, it was not unexpected since the parent diol is known to be much more susceptible to aromatisation than the corresponding acetonide-protected derivative.

An examination of the literature suggested that that the efficiency of the IMDA cycloaddition reactions of the type described above could be improved by increasing the flexibility of the tethers. Mihovilovic *et al.* have also reported examples of IMDA cycloaddition reactions of *c*-DHC derivatives where the IMDA cycloaddition reaction is competing against a dimerisation reaction of the precursors.[33] In this work, it was observed that the flexibility of the tether was more important for the success of the reaction than activation of the dienophile. For example, when compound **53c** was refluxed in toluene, no IMDA product was obtained and only polymerisation and dimerisation products were observed. In contrast, precursor **53d**, despite possessing a less activated dienophile, gave almost quantitative yields of the cycloadduct **54d** (Scheme 3.29). This outcome is attributed to the increased flexibility of the side chain in compound **53d** as compared with that in congener **53c**.



Scheme 3.29: *Reagents and conditions* (i) toluene, reflux, 3 to 7 days.

To this end, compounds **236** and **248** were treated with sodium borohydride to effect reduction of the side-chain carbonyl moieties. The corresponding alcohols, **253** and **254** respectively, were obtained in good yields and as a *ca.* 1:1 mixture of diasteriomers (as determined by GCMS) (Scheme 3.30).

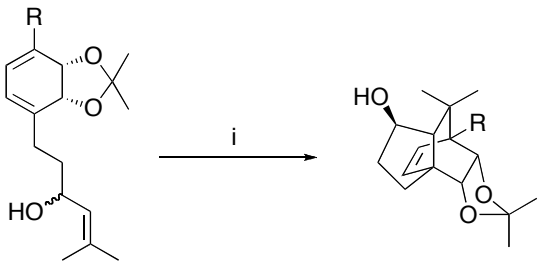


236 R = H
248 R = Me

253 R = H (84%)
254 R = Me (83%)

Scheme 3.30: *Reagents and conditions* (i) $NaBH_4$ (2.0 mole equiv.), MeOH, 0 to 18 ºC, 2 h.

With the desired alcohols in hand, the IMDA cycloaddition reactions of these compounds were attempted. Each substrate was heated in refluxing mesitylene in the presence of a catalytic amount of BHT and, in both cases, after 4 days the starting materials had been consumed and a single Diels-Alder adduct had formed (Scheme 3.31). Disappointingly, the yield obtained for the IMDA cycloaddition reaction of alcohol **253** (44%) was less that arising from the corresponding carbonyl compound, **236** (52%). However, a pronounced improvement was observed for the IMDA precursor that possesses substitution on both the diene and dienophile. Thus, while compound **248** (possessing the carbonyl moiety) would not undergo the desired cycloaddition reaction (Entry 4, Table 3.2), the corresponding alcohol **254** afforded cycloadduct **256** in 46% yield.



253 R = H
254 R = Me

255 R = H (44%)
256 R = Me (46%)

Scheme 3.31: *Reagents and conditions* (i) BHT (0.1 mole equiv.), mesitylene, reflux, 4 days.

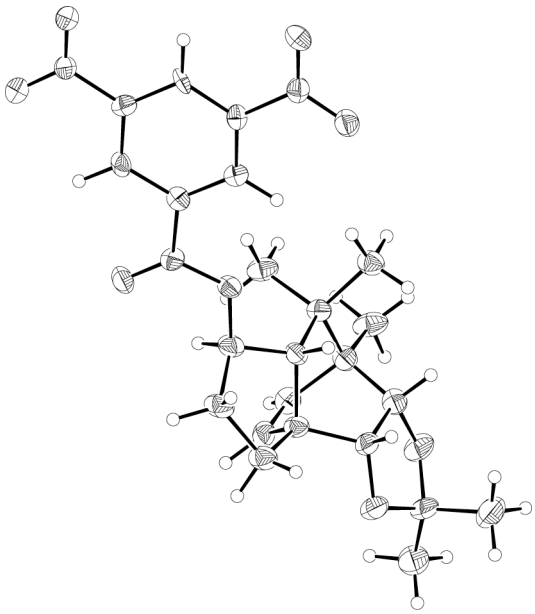


Figure 3.16: *Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of the 3,5-dinitrobenzoyl derivative of alcohol* ***256****.*

It was surprising to find that, despite IMDA precursors **253** and **254** being mixtures of diasteriomers, a single diasteriomer of the IMDA product was obtained in each case. Given that the yield is less than 50% in both instances, one possible explanation is that only one diastereomer is participating in the Diels-Alder reaction and the other is decomposing. However, this has not yet been confirmed and studies directed towards understanding this result are continuing.

In order to unambiguously determine the stereochemistry at C6 in alcohol **256,** the compound was converted into the corresponding 3,5-dinitrobenzoate derivative and its structure was determined by single-crystal X-ray analysis (Figure 3.16, Appendix 12). In this manner, it was established that the hydroxy group of compound **256** is in the *exo*-position. Since an X-ray crystal structure of alcohol **255** (or a suitable derivative) could not be obtained, the assignment of the C6 stereochemistry was made by analysis of the ^{1}H NMR spectrum. Comparison of ^{1}H NMR spectra of alcohols **256** (Figure 3.17) and **255** (Figure 3.18) revealed that the signals relevant to assignment of the C6 stereochemistry, namely those arising from C5a-H and C6-H, are very similar for the two compounds. The signals due to the oxymethine proton (C6-H) appear at the same position, *ca.* δ 3.85, in the spectra of both alcohols. Furthermore, in both spectra the doublets assigned to the C5a proton are in similar positions and have similar coupling constants, δ 1.23 (J = 9.3 Hz) and δ 1.23 (J = 8.1 Hz), for alcohol **255** and **256**, respectively. Both of these coupling constants are consistent with the C5a and C6 protons possessing a trans relationship as determined by the Karplus curve.[150] In this manner, it was determined that both alcohols possess the same (C6) stereochemistry.

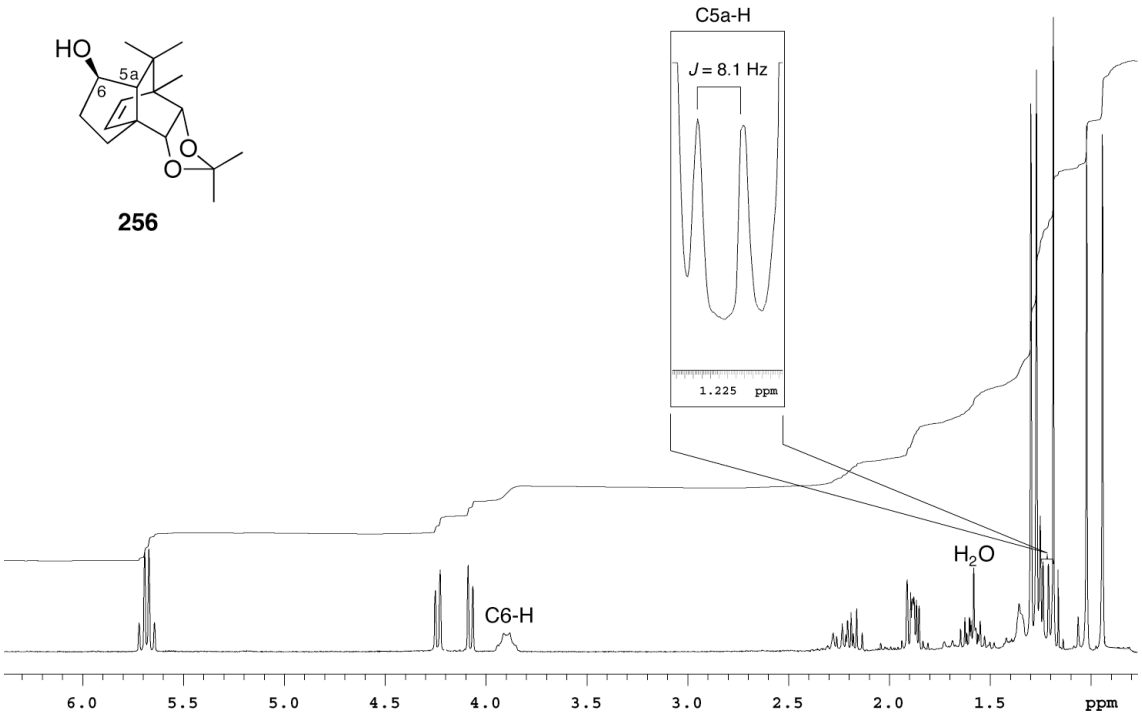


Figure 3.17: *300 MHz ^{1}H NMR spectrum of alcohol **256** (recorded in $CDCl_3$).*

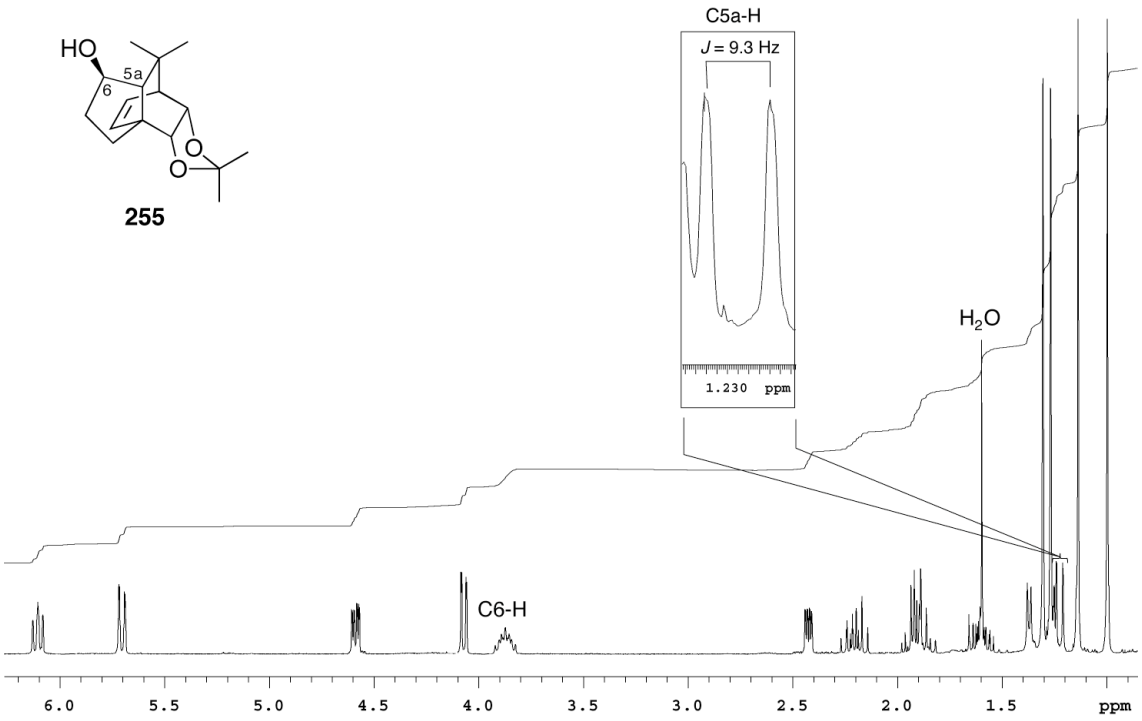


Figure 3.18: *300 MHz ^{1}H NMR spectrum of alcohol **255** (recorded in $CDCl_3$).*

3.7 Conclusions

This Chapter details the synthesis of several novel *c*-DHC derivatives and their participation in IMDA cycloaddition reactions. These studies have given an insight into the stereoselectivities associated with the IMDA cycloaddition reactions of *c*-DHCs and the types of frameworks accessible *via* this process. The following observations should be reiterated:

- The union of the *c*-DHC moiety and the dienophilic tether can be achieved *via* two distinct protocols; namely a palladium-catalysed Negishi cross-coupling or a conjugate addition reaction. These procedures should allow the preparation of a range of substituted *c*-DHC derivatives that cannot currently be accessed, either by microbial transformation or by the coupling methods that have been reported to date.

-IMDA reactions of unprotected *c*-DHC derivatives were found to proceed with excellent facial selectivity, *via syn*- addition, but with essentially no diastereoselectivity, affording a mixture of *endo*- and *exo*- adducts.

-IMDA reactions of acetonide protected *c*-DHC derivatives occurred diastereoselectively, *via* an *endo*-transition state, but with essentially no facial selectivity, affording both *syn*- and *anti*-adducts.

-The *anti*-selectivity of the IMDA reactions could be improved by increasing the steric demands on the system. This could be achieved either by using a bulky protecting group on the *c*-DHC, or by introducing substitution on the diene and/or the dienophile.

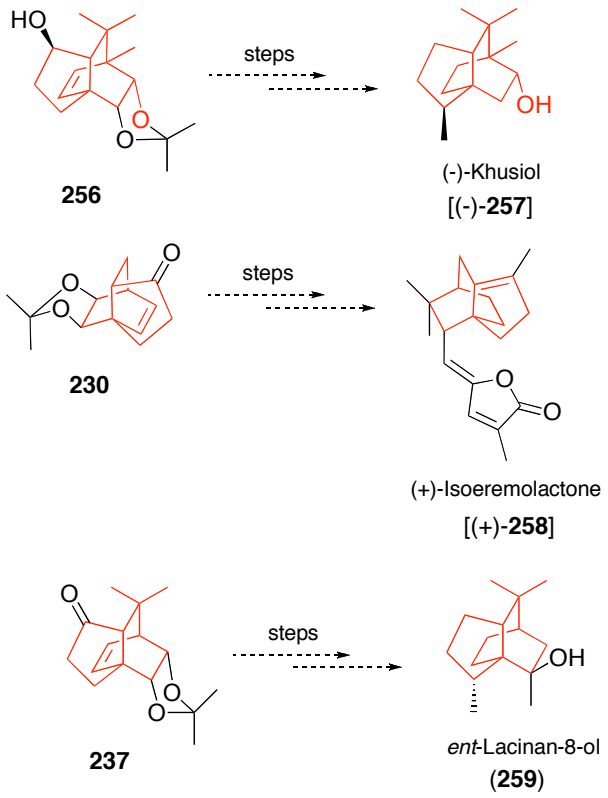
-Dimerisation of the IMDA precursors was found to be a competing process when the systems were highly substituted. In these instances, the efficiency of the IMDA reaction could be improved by increasing the flexibility of the tether. In this manner, cycloadducts possessing two contiguous quaternary centres were prepared.

3.8 Future Work

Future aspects of this project will be directed towards exploiting the IMDA cycloaddition reaction of *c*-DHC derivatives for the total syntheses of a range of biologically relevant natural products. The following Sections present possible targets and strategies for obtaining them.

3.8.1 Proposed access to terpenoid natural products by elaboration of IMDA cycloadducts

Tricyclic systems possessing annulated bicyclo[2.2.2]octane frameworks are present in a number of natural product families, such as the khusianes,[151,152] ermolactones,[153,154] lacinanes[155] and dupreziananes.[156] The cycloadducts described in this Chapter embody the core structures of these natural products, as well as possessing the correct substitution patterns in a number of cases. Scheme 3.32 highlights examples of natural products that it is envisioned could be readily accessed by elaboration of the relevant IMDA cycloadducts.



Scheme 3.32: *Proposed access to various terpene natural products from Diels-Alder adducts* ***256, 230*** *and* ***237****.*

One particularly compelling target is the neurotrophic factor (-)-*O*-11-debenzoyltashironin [(-)-**260**] (Figure 3.19).[157,158] Both the interesting biological activity and the complex molecular architecture of this compound makes developing a synthesis of compound **260** an ideal means of highlighting of the versatility of the protocols detailed earlier in this Chapter.

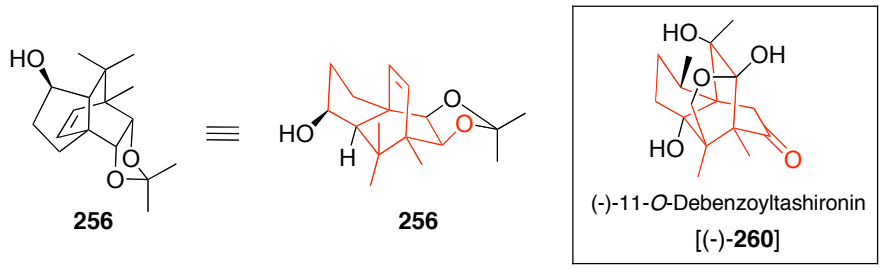


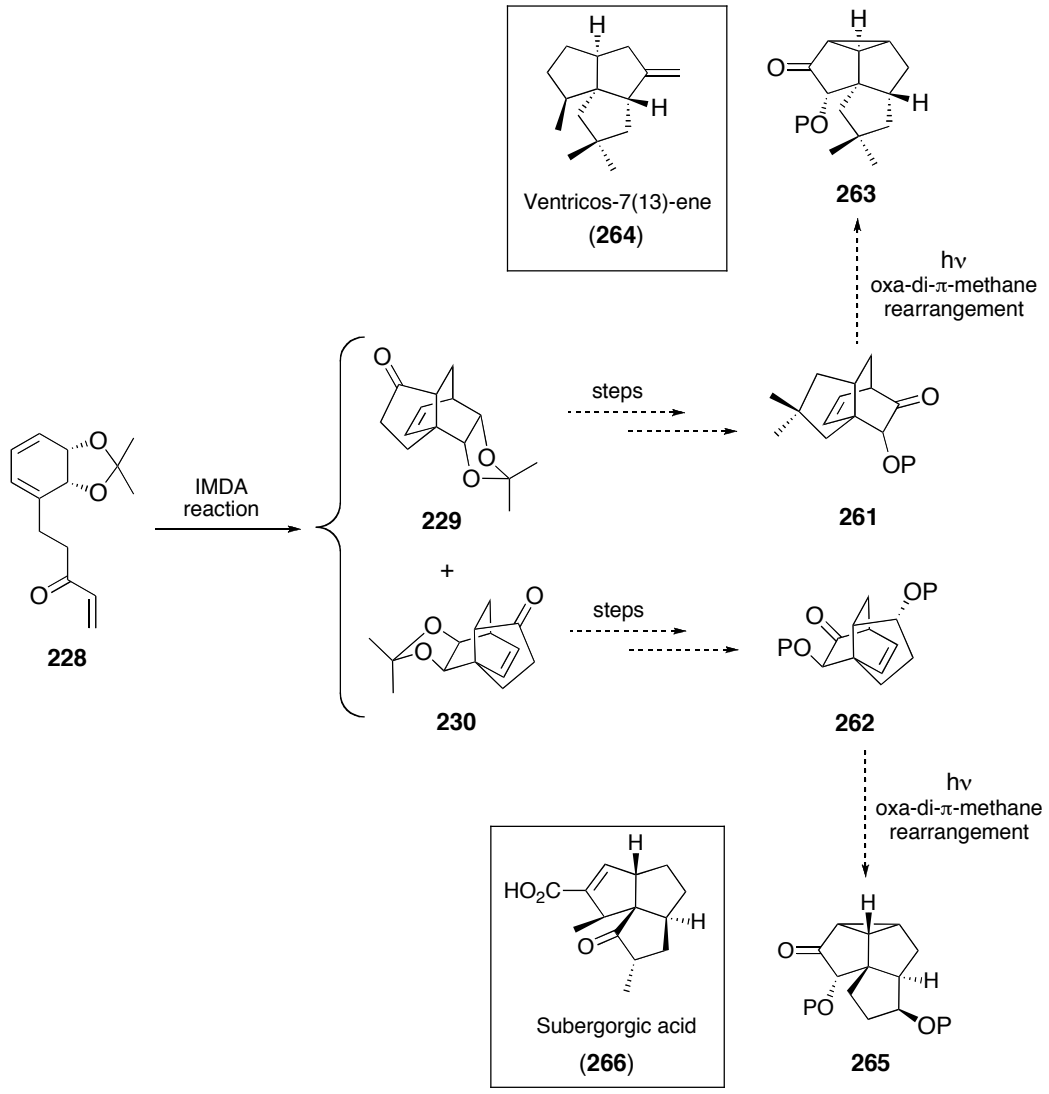
Figure 3.19: *The core structure of (-)-11-*O*-debenzoyltashironin [(-)-**260**] as possessed by compound **256**.*

3.8.2 Proposed access to sesquiterpenoid natural products *via* a combination of IMDA cycloadditions reactions and photochemical rearrangements

The versatility of the cycloadducts prepared by the protocols described in this Chapter is further highlighted when their potential to act as substrates in photochemical rearrangements (such as that used in Chapter Two) is considered. This Section presents a selection of sesquiterpene natural products that might be accessed utilising a combination of the chemistries presented in Chapters Two and Three.

Diels-Alder adducts **229** and **230**, produced during the IMDA reaction of enone **228**, are pseudo-enantiomeric, meaning that, following the appropriate manipulations, both enantiomeric series of a target molecule can, in principle, be accessed. This feature of the IMDA cycloaddition reactions of *c*-DHC derivatives is particularly useful in the synthesis of natural products, especially where the absolute stereochemistry of the target compound has not yet been established, or when synthesising compounds from a class of natural products that possess members in both enantiomeric series. A pertinent example of such a class is the angular triquinane family. It is envisioned that Diels-Alder adducts **229** and **230** could be converted, *via* a series of standard functional group interconversions, into β,γ-unsaturated ketones **261** and **262**, respectively (Scheme 3.33). Triplet sensitised irradiation of both of these compounds should then effect formation of the oxa-di-π-methane rearrangement products **263** and **265**. At this stage the enantiomeric relationship between these compounds is clearly apparent. Reductive

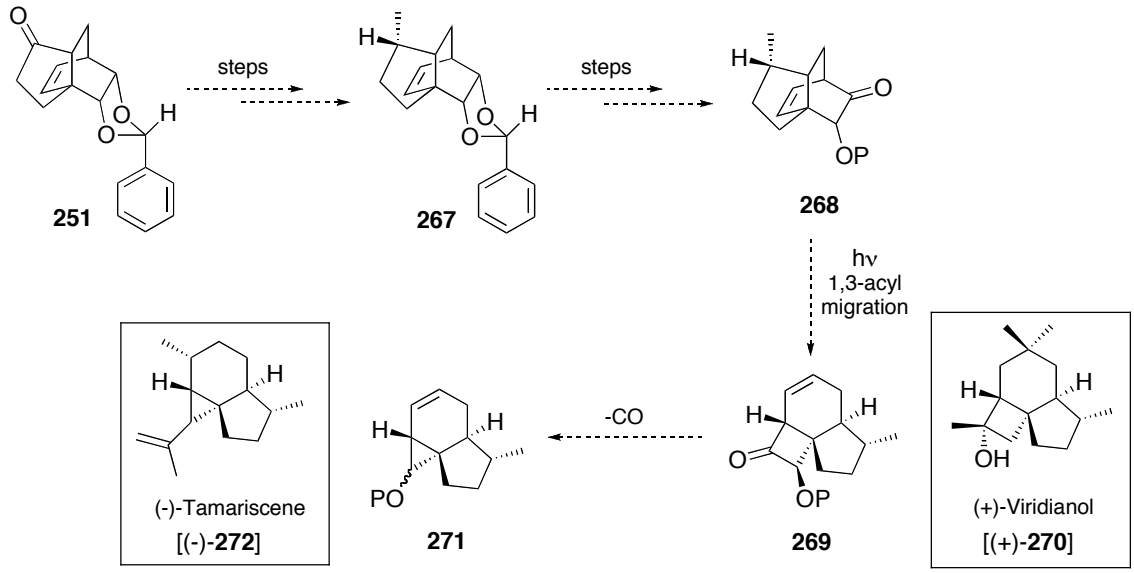
cleavage of the peripheral cyclopropane bond of each compound should then generate the corresponding tricyclic systems, which encompass the core structures of the triquinane natural products ventricos-7(13)-ene (**264**)[159] and subergorgic acid (**266**).[160,161]



Scheme 3.33: *Proposed access to angular triquinane-type natural products of either enantiomeric series.*

A similar strategy could be applied to the synthesis of the novel sesquiterpenoids viridianol [(+)-**270**][162] and tamariscene [(-)-**272**] (Scheme 3.34).[163] In this case *endo*-, *anti*-adduct **251** possesses the desired stereochemistry for the synthesis of both natural products. Elaboration of the cycloadduct **251** to the β,γ-unsaturated ketone **268**, and subsequent irradiation, (this time under direct irradiative photochemical reaction conditions) should afford cyclobutanone **269**

and/or the cyclopropane **271** (*via* spontaneous decarboxylation). Each of these photoproducts closely resembles the tricyclic frameworks assigned to the target natural products.



Scheme 3.34: *Proposed access to (-)-tamariscene and (+)-viridianol.*

The broad range of targets that is likely to be accessible by exploiting the IMDA cycloaddition of *c*-DHC derivatives serves to highlight the importance of the protocols presented in this Chapter. A pertinent example of this is presented in the following Chapter wherein a formal total synthesis of the potent antibacterial agent platencin,[164] which utilizes this IMDA cycloaddition reaction as the key step, will be discussed.

CHAPTER FOUR

Formal Total Synthesis of (-)-Platencin

4.1 Introduction

4.1.1 Isolation and structure of (-)-platencin

In 2007 Singh and co-workers, based at the Merck Research Laboratories in New Jersey, described the isolation of (-)-platencin [(-)-**92**] from a strain *Steptomyces platensis* MA7339 found in a soil sample collected in Spain.[164] This discovery was made *via* high-throughput screening of natural product extracts using a target-based, whole-cell approach that was developed by these researchers in their quest for new antibiotic agents with novel modes of action.[165] The use of this assay had, a year earlier, led to the identification of (-)-platensimycin [(-)-**273**],[166] a related natural product that attracted considerable attention due to its potent activity against many antibiotic-resistant bacteria.[167-171]

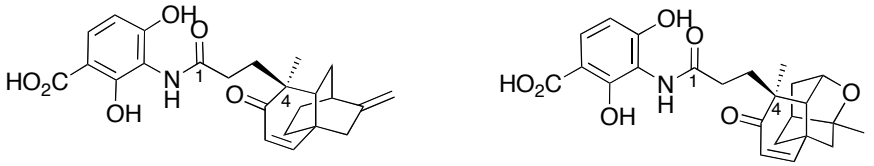


Figure 4.1: *Target compound (-)-platencin and the related compound (-)-platensimycin.*

(-)-Platensimycin and (-)-platencin are structurally and biologically related. Both compounds are comprised of two structurally distinct subunits, namely a 3-amino-2,4-dihydroxybenzoic acid moiety, which is common to both, and this is linked, *via* an amide bond, to a lipophilic domain that is unique to each compound. While the core of platensimycin consists of a tetracyclic motif incorporating a cyclic ether, (-)-platencin possesses a tricyclic core devoid of ring oxygens.[172,173]

Although (-)-platensimycin and (-)-platencin were initially isolated from different strains of *S. platensis*, they have since been co-isolated.[174] This observation suggests that they share a common biosynthetic pathway. Following feeding studies, Singh and co-workers have proposed that a non-mevalonate terpeniod pathway is involved in the synthesis of the core structure of both compounds, while an intermediate from the citric acid cycle and phosphoenolpyruvate (PEP) are utilized in the biogenesis of the aromatic unit.[174,175]

4.1.2 Biological properties of (-)-platencin

The increasingly significant problem of antibacterial resistance has prompted a world-wide search for new types of antibiotics that function *via* novel modes of action. As a consequence, the discovery of (-)-platensimycin and (-)-platencin, which act *via* a mechanism unexploited by established antibiotics, has generated much interest. The mode of action of these compounds is *via* inhibition of β-keto-acyl-(acyl-carrier-protein) synthase (KAS) enzymes that are involved in bacterial fatty acid biosynthesis. This is an essential metabolic process that bacteria require for the assembly of their cell membranes.[176] While (-)-platensimycin is a selective inhibitor of the enzyme FabF (KAS II),[164] (-)-platencin exhibits dual activity, inhibiting both FabF (KAS II) and FabH (KAS III).[166] As these enzymes are highly conserved among pathogens, both compounds exhibit broad-spectrum antibacterial properties. Furthermore, since this mode of action is unique and not, therefore, targeted by any existing antibiotics, these compounds show no cross-resistance and are active against all key drug-resistant bacterial strains. Specifically, both compounds exhibit activity against key Gram-positive pathogens such as MRSA (methicillin-resistant *Staphylococcus aureus*) and VRE (vancomycin-resistant *Enterococci*) as well as linezolid-resistant and macrolide–resistant pathogens. However, (-)-platencin shows the greater antibacterial activity against vancomycin-resistant *Enterococcus faecium* and efflux-negative *Escherichia coli*.[164]

The ability of (-)-platencin to inhibit two enzymes on the same pathway not only makes it more active than (-)-platensimycin but should also result in a lower resistance potential. Thus, it would seem that it is the more attractive lead compound for the development of new antibiotics. Unfortunately, like (-)-platensimycin, (-)-platencin has poor *in vivo* activity unless administered by continuous infusion. This situation is attributed to its poor pharmacokinetic properties.[164] These properties could potentially be improved by chemical modification. However, the first step in the production of more active (-)-platencin analogues is to develop a strategy for the synthesis of the parent molecule. As such, this Chapter presents the development of a new and enantioselective route to (-)-platencin that should allow for the synthesis of novel antibacterial analogues.

4.2 Previous Studies on the Synthesis of (-)-Platencin

4.2.1 Overview

Owing to the novel structure and remarkable biological properties of (-)-platencin, it has attracted significant attention from the synthetic community. The first total synthesis of (-)-platencin was reported by Nicolaou and co-workers in early 2008.[48] This was promptly followed by reports from a number of other groups, such that seven total[48,49] or formal total[177-181] syntheses of platencin have been published this year.⊕ Four of these syntheses, which are particularly outstanding and/or relevant to the work detailed in this Thesis, are described below.#

4.2.2 Total and formal total syntheses

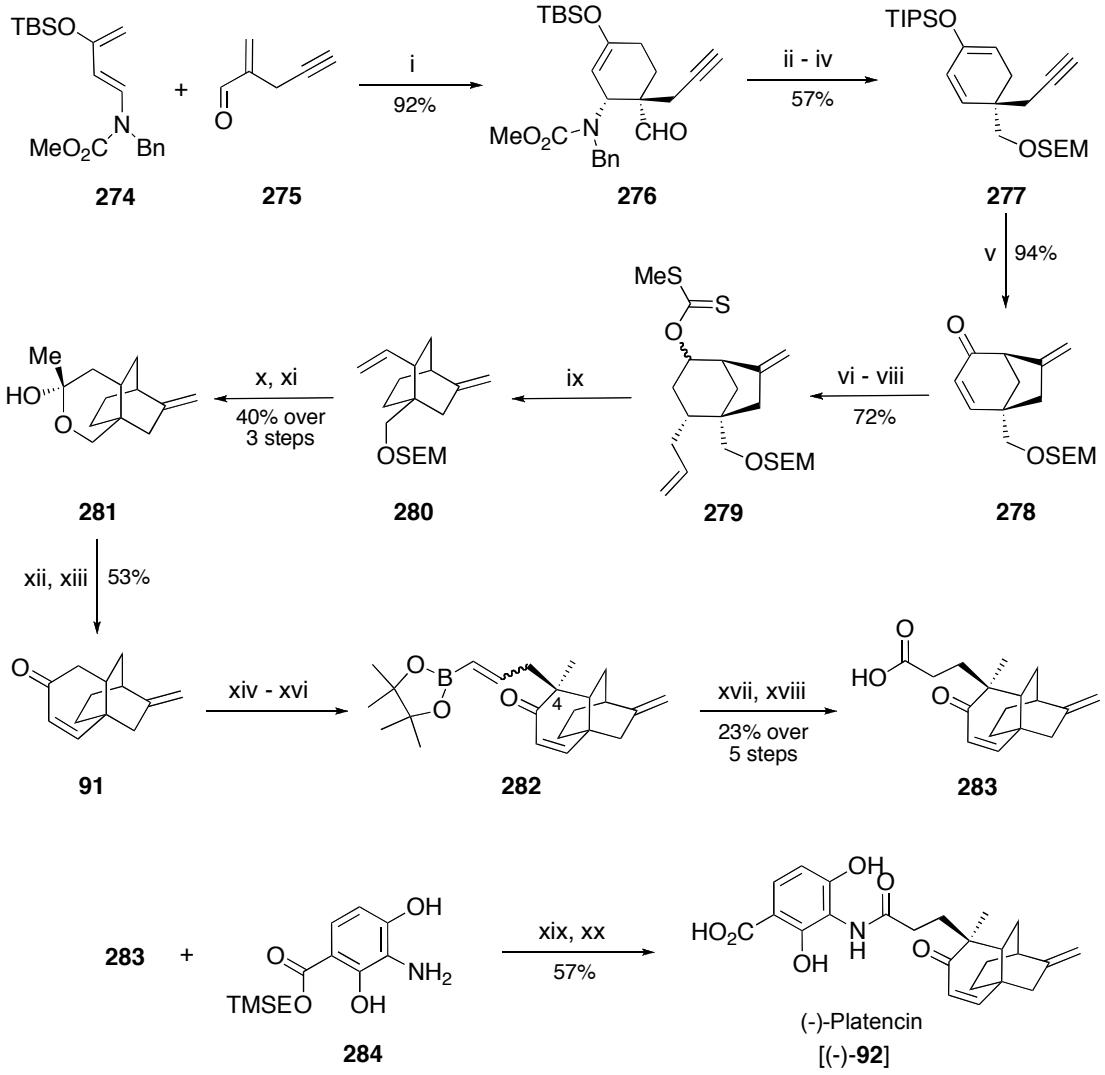
Nicolaou's asymmetric synthesis of (-)-platencin (2008)

Nicolaou and co-workers[48] reported the first synthesis of (-)-platencin just eight months after the paper detailing its isolation and structure was published. Their approach employed an asymmetric intermolecular Diels-Alder reaction, a gold-catalysed cyclisation process and a homoallyl radical cyclisation as the key steps in the construction of the core structure **91** (Scheme 4.1). The installation of the propionamide-linked anilide unit was achieved using protocols analogous to those employed in the synthesis of (-)-platensimycin.[182,183]

The synthesis of the key structure, **91**, commenced with a Rawal-type asymmetric Diels-Alder reaction[184] between the known 1-amino-3-siloxy-diene **274** and acetylenic aldehyde **275** (synthesised in one pot from 4-pentyn-1-ol in 53% yield), which afforded cyclohexene **276** in 92% yield and *ca*. 93% ee. Reduction of the aldehyde moiety, followed by exposure of the ensuing alcohol to aqueous HCl, generated the corresponding hydroxy-enone that was then protected as the SEM ether. Exposure of this last compound to tri*iso*propylsilyl triflate (TIPSOTf) generated silyl enol ether **277**, the substrate for the key gold-catalysed cyclisation reaction. Thus, exposure of acetylenic diene **277** to the gold catalyst derived from [$AuCl(PPh_3)$] and $AgBF_4$ brought about the desired cyclisation, affording bicyclic enone **278** in excellent yield (94%). Conjugate addition of the cuprate derived from allylmagnesium chloride to the enone moiety was followed by reduction of the residual ketone and thereby generating a 2:1 mixture of diastereomeric alcohols. These were then converted into the corresponding xanthate esters **279** (2:1 mixture of diastereomers). The pivotal homoallylic radical rearrangment

⊕ Reference 181 refers to the publication of the synthesis detailed in this Chapter.
These syntheses were all published during the course of this research.

proceeded smoothly on exposure of the mixture of xanthate esters (**279**) to AIBN and tri-*n*-butyltin hydride to afford bicyclo[2.2.2]diene **280**. Wacker oxidation of diene **280** followed by deprotection of the SEM protected primary alcohol afforded the corresponding hydroxy-ketone that was found to exist, preferentially, as hemiacetal **281**. Finally, oxidation of compound **281** and subsequent aldol condensation of the ensuing keto-aldehyde generated enone **91**, the key precursor to the target molecule.



Scheme 4.1: *Reagents* (i) Cr(III)-salen complex catalyst; (ii) a) $LiAlH_4$; b) HCl; (iii) SEMCl, Et_3N, DMAP; (iv) TIPSOTf, Et_3N; (v) $[AuCl(PPh_3)]$, $AgBF_4$; (vi) allylmagnesium chloride, $CuBr{\cdot}Me_2S$; (vii) $NaBH_4$; (viii) CS_2, KHMDS, MeI; (ix) *n*-Bu_3SnH, AIBN; (x) $PdCl_2$, CuCl, O_2; (xi) TASF, DMPU; (xii) TPAP, NMO; (xiii) NaOH; (xiv) KHMDS, MeI; (xv) KHMDS, allyl iodide; (xvi) Hoveyda-Grubbs II cat., benzoquinone; (xvii) Me_3NO; (xviii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (xix) HATU, Et_3N; (xx) TASF.

The conversion of enone **91** into (-)-platencin began with the diastereoselective installation of the methyl and propionic acid groups. To this end, compound **91** was sequentially alkylated with methyl iodide then allyl bromide. Due to the rigid structure of the molecule alkylation occurred selectively at the *exo*-face to generate the desired stereochemistry at C4. The resulting triene underwent regioselective cross-metathesis at the newly installed allyl olefin, in the presence of Hoveyda-Grubbs' catalyst and benzoquinone, with vinyl-pinacol boronate ester to afford boronate **282**, as a *ca*. 3:1 mixture of *E/Z* isomers. This mixture of boronates was oxidised, *via* the corresponding aldehyde, to carboxylic acid **283** thereby completing installation of the propionic acid unit. Amide coupling of compound **283** with aniline **284** was achieved using HATU as the coupling reagent and deprotection of the ensuing TMSE ether derivative afforded (-)-platencin.

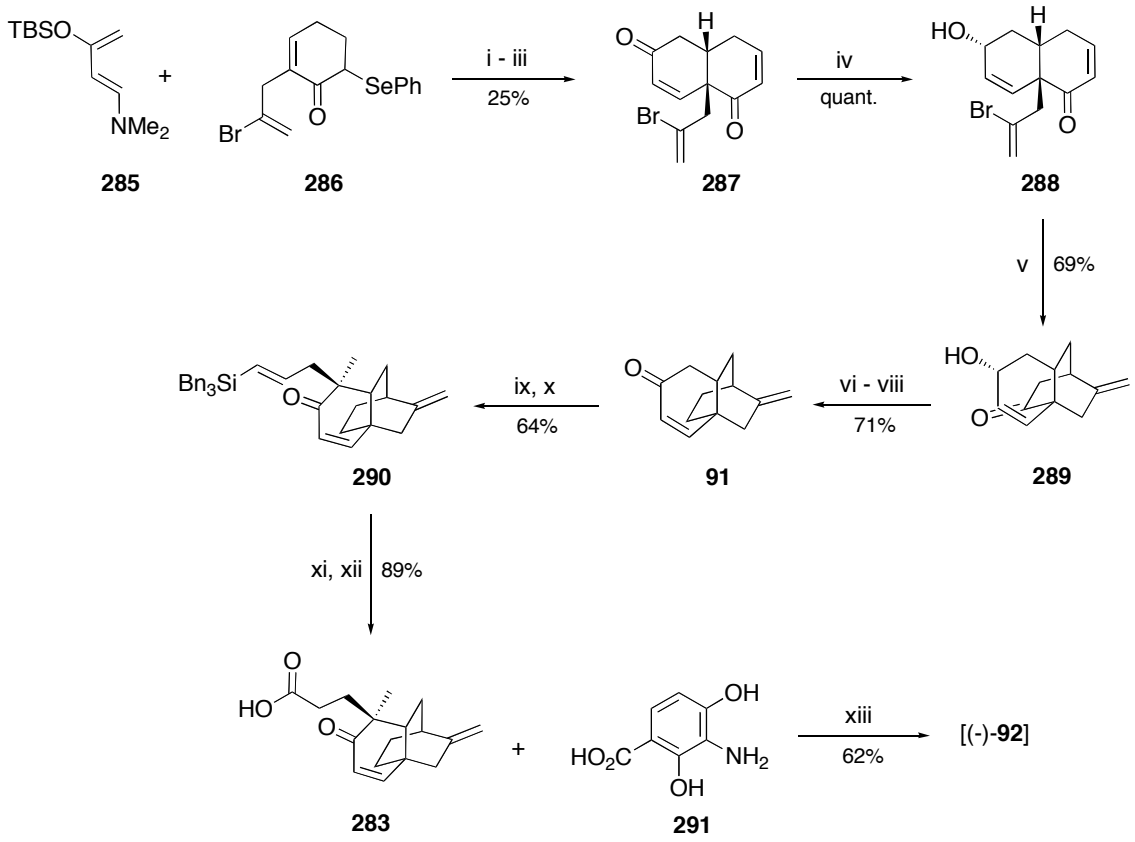
Rawal's total synthesis of (±)-platencin (2008)

The synthetic route to platencin published by Rawal *et al*.[49] (Scheme 4.2) made use of this group's cycloaddition methodology by employing a 1-amino-3-siloxy-diene derivative as a highly reactive diene in a challenging Diels-Alder reaction. These reagents had previously been developed as effective substitutes for electron-rich dienes and shown to readily participate in Diels-Alder reactions without the need for Lewis-acid activation or high temperatures.[Ψ] Thus, an uncatalysed Diels-Alder reaction between diene **285** and cyclohexanone **286** (prepared from *O*-anisic acid in 37% yield over 2 steps) and subsequent selenoxide formation and elimination afforded the racemic modification of bisenone **287**. Regio- and stereo-selective reduction of the less hindered carbonyl group delivered alcohol **288**, which served as the substrate for the second key process in this synthetic sequence, namely a Ni-promoted reductive cyclisation reaction. Treatment of compound **288** with $[Ni(cod)_2]$ promoted a 5-*exo*-trig cyclisation of the alkenyl bromide onto the enone moiety, thus generating compound **289** which embodies the desired methylenebicyclo[2.2.2]octane framework. Removal of the ketone, *via* the corresponding tosyhydrazone, and oxidation of the allylic alcohol afforded enone **91**, embodying the core structure of platencin.

Rawal and co-workers next focused on the development of a concise route to the natural product from this key intermediate. Alkylation of enone **91** with methyl iodide, followed by allylation with (*E*)-1-tribenzyl-silyl-3-iodo-prop-1-ene, gave compound **290** in a completely diastereoselecive manner. Oxidation of the vinyl silane (using a modification of the Fleming-Tamao protocol) afforded the corresponding aldehyde that was readily converted, using a Lindgren-Kraus oxidation, into carboxylic acid **283**. This sequence proved to be both

Ψ Rawal *et al.* also pioneered the asymmetric variant of this reaction,[184] which was used by Nicolaou in the synthesis described above.

shorter and higher yielding (4-steps *vs* 5-steps, 57% *vs* 23%) than that reported by Nicolaou *et al*.[48] Direct amide coupling of the fully unprotected anilide fragment **291** using DCC and DMAP then completed the reaction sequence and delivered (±)-platencin in 62% yield.

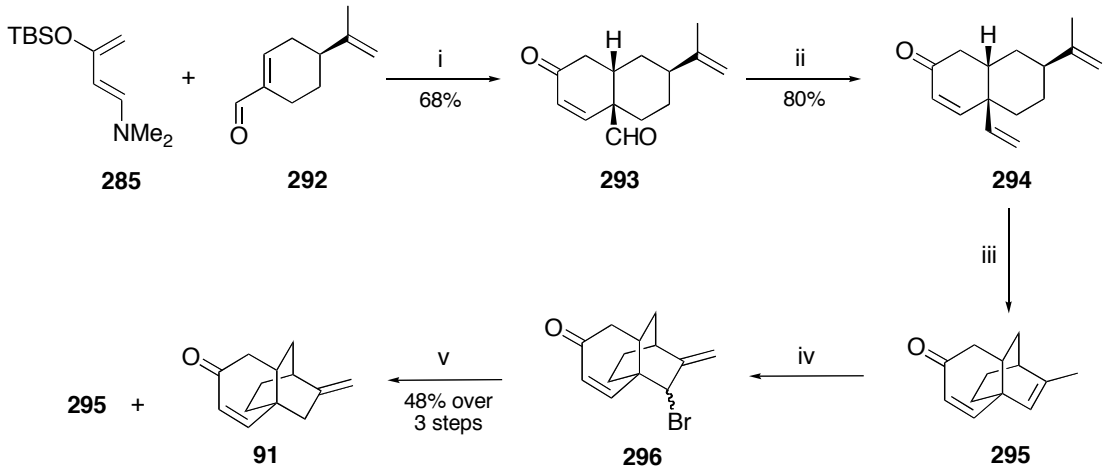


Scheme 4.2: *Reagents* (i) 40 ºC; (ii) aq. HF; (iii) H_2O_2, pyridine; (iv) DIBAL-H; (v) $[Ni(cod)_2]$, cod; (vi) *p*-TsOH, $TsNHNH_2$; (vii) $NaBH_3CN$, $ZnCl_2$; (viii) MnO_2; (ix) KHMDS, MeI; (x) KHMDS, (*E*)-1-tribenzylsilyl-3-iodo-prop-1-ene; (xi) TBAF, iodosobenzene, H_2O_2, $KHCO_3$; (xii) $NaClO_2$, NaH_2PO_4, 2,3-dimethylbutene; (xiii) DCC, DMAP, Et_3N.

Mulzer's formal total synthesis of (-)-platencin (2008)

Remarkable brevity is the signature feature of the five-step, protecting-group-free synthesis of the core of (-)-platencin reported recently by Mulzer *et al.* (Scheme 4.3).[178] This route utilised a Diels-Alder cycloaddition reaction between the Rawal diene **285** and commercially available (-)-perillaldehyde (**292,** >92% ee) to afford, after acid hydrolysis, bicylic enone **293** possessing all three stereocentres associated with the platencin core. The third ring was then formed *via* ring closing metathesis of triene **294** (prepared from cycloadduct **293** by Wittig methylenation) in the presence of Grubbs' second-generation catalyst to produce the desired bicyclo[2.2.2]octane framework of compound **295**. Finally, isomerization of the endocyclic

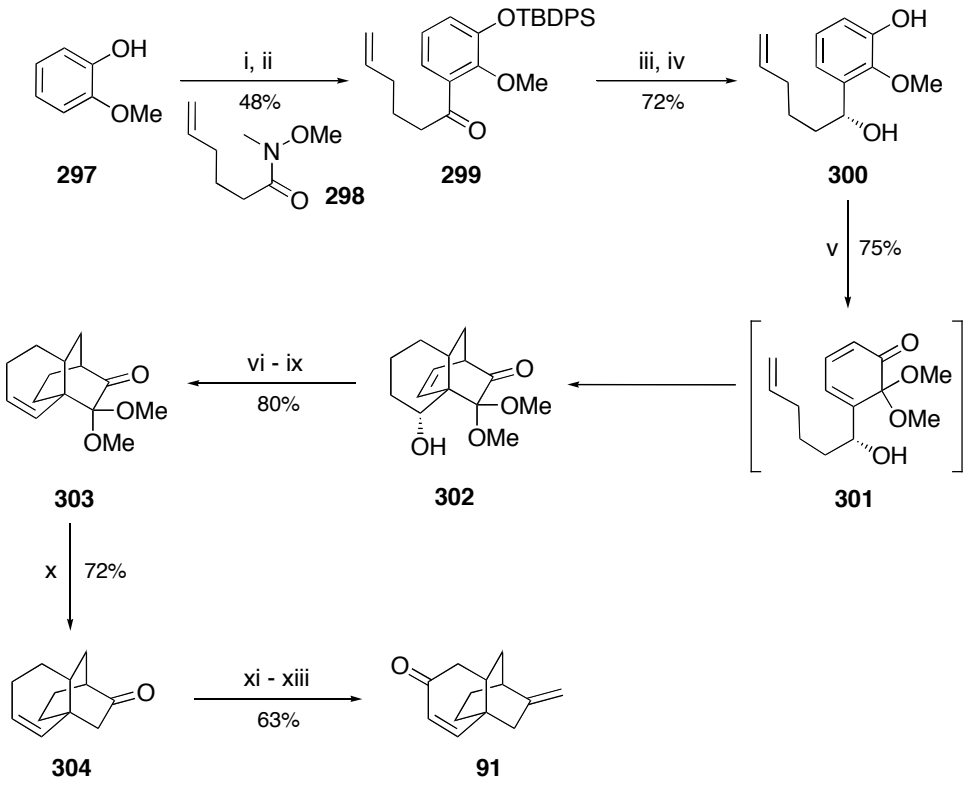
double bond to the exocyclic position was achieved by a two step procedure involving allylic bromination and chromium (III)-mediated reduction to afford the core of (-)-platencin, thereby completing the most concise route to compound **91** reported to date.



Scheme 4.3: *Reagents* (i) a) 110 ºC; b) aq. HCl; (ii) $Ph_3P{=}CH_2$; (iii) 2nd Gen. Grubbs' cat.; (iv) NBS; (v) $CrCl_3$, $LiAlH_4$.

Chen and Nicolaou's formal total synthesis of (-)-platencin (2008)

The formal total synthesis of (-)-platencin reported by Chen and Nicolaou[180] (Scheme 4.4) utilised an IMDA reaction to generate the tricyclic core structure of the target molecule in a single step. The first stage of the synthesis was concerned with the preparation of an enantiopure substrate for the key IMDA reaction. To this end, protection of guaiacol (**297**) as the TBS ether allowed for *ortho*-lithiation and subsequent reaction with Weinreb amide **298** to afford ketone **299**. Asymmetric reduction of the latter compound under Corey-Bakashi-Shibata (CBS) conditions, followed by desilylation, delivered benzyl alcohol **300** in 90% ee. Generation of the desired substrate was then achieved by oxidation of benzyl alcohol **300** with $PhI(OAc)_2$ to afford *o*-benzoquinone **301**. This immediately underwent a stereoselective IMDA reaction to give cycloadduct **302** as the major product. The high level of selectivity observed for this reaction is quite remarkable considering that it was controlled by a single stereocentre. With the construction of the bicylo[2.2.2]octane framework complete, standard functional group manipulations were used to convert compound **302** into the platencin core (**91**).

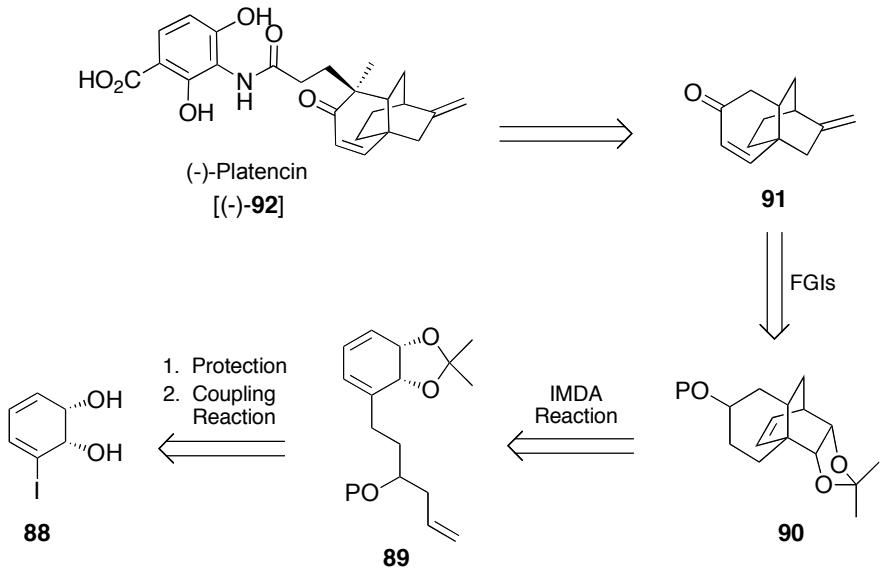


Scheme 4.4: *Reagents* (i) TBDPSCl, imidazole, DMAP; (ii) *s*-BuLi, TMEDA, **298**; (iii) (*S*)-(-)-2-methyl-CBS-oxazaborolidine, catechol borane; (iv) TBAF; (v) a) $PhI(OAc)_2$, $KHCO_3$; b) 110 ºC; (vi) Pd on C, H_2; (vii) PCC; (viii) $PhNTf_2$, KHMDS; (ix) $Pd(PPh_3)_2Cl_2$, *n*-Bu_3N, HCO_2H; (x) SmI_2, MeOH; (xi) MeMgBr; (xii) $Mn(OAc)_3$, *t*-BuOOH, O_2; (xiii) Martin's sulfurane.

4.3 Retrosynthetic Analysis and Strategy

It was envisioned that by exploiting the methodologies described in the previous Chapter, namely the IMDA reaction of a *c*-DHC derivative, the basic framework of (-)-platencin could be synthesised in a particularly efficient manner. The appropriate retrosynthetic analysis of target (-)-**92** is shown in Scheme 4.5 and involved initial detachment of the two side-chain residues of the molecule from the tricyclic core structure giving enone **91**; a known precursor to (-)-platencin.[48,49] It was anticipated that this key structure could, in turn, be derived from Diels-Alder adduct **90** using standard procedures. Compound **90** is the expected product of a stereoselective IMDA reaction of precursor **89**, wherein the acetonide protecting group on the diol moiety should ensure the cycloaddition occurs with *anti*-selectivity. This outcome is crucial to ensuring the cycloadduct possesses the correct absolute stereochemistry required for the natural product. It was anticipated that compound **89** could, in turn, be obtained by a coupling

reaction between the acetonide-protected derivative of *c*-DHC **88** and an appropriate 6-carbon partner possessing a dienophilic moiety.



Scheme 4.5: *Retrosynthetic analysis of (-)-platencin [(-)-**92**]*

The successful implementation of this strategy as part of establishing a formal total synthesis of (-)-platencin (through the aquisition of compound **91**) is discussed in the following Sections and serves to highlight the synthetic utility of the protocols described in the previous Chapter, namely the IMDA reaction of *c*-DHCs, for the synthesis of natural products.

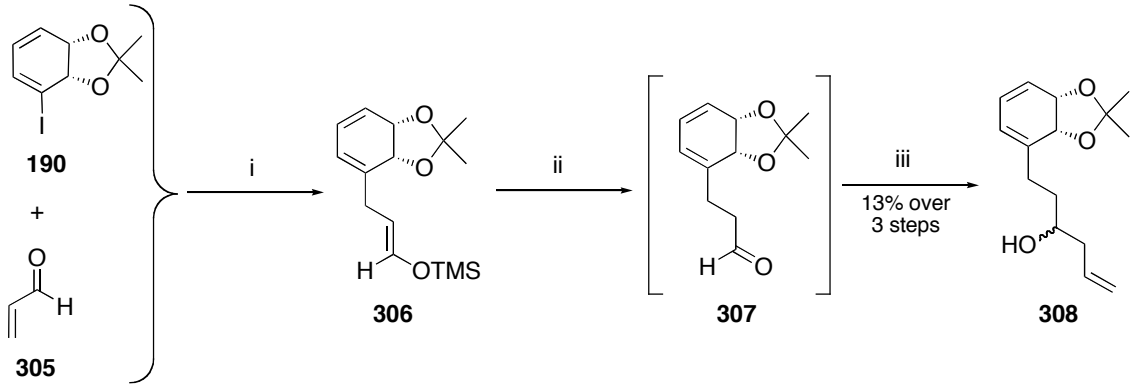
4.4 Formal Total Synthesis of (-)-Platencin

4.4.1 Synthesis of IMDA precursor 89

4.4.1.1 Michael addition approach

The previous Chapter detailed how *c*-DHC **190** could be engaged in a conjugate addition reaction with various enones to deliver a number of derivatives. As such, it was anticipated that a similar approach could be used for the synthesis of the desired substrate for the IMDA reaction, namely *c*-DHC **89**. To this end, and following the protocols defined in Chapter Three, the acetonide-protected *c*-DHC **190** was treated with *i*-PrMgCl (to generate the corresponding Grignard reagent) then CuBr•SMe_2 and HMPA (Scheme 4.6). A mixture of acrolein **305** and TMSCl[145,146] was then added dropwise to the ensuing reaction mixture. While tlc analysis of the reaction mixture suggested that the expected 1,4-addition process had taken place to generate

silyl enol ether **306**, when the reaction mixture was worked up using standard protocols (quench with a saturated aqueous solution of NH_4Cl, followed by drying of the separated organic fractions with Na_2SO_4 or $MgSO_4$) the desired aldehydic product **307** was not generated. Instead, a mixture of decomposition products was obtained as judged by ^1H NMR analysis of the crude reaction mixture. Following extensive investigations it was established that the 1,4-addition reaction proceeds smoothly, generating silyl enol ether **306** as the sole product. However, on hydrolytic workup of the reaction mixture, the ensuing aldehyde (**307**) rapidly decomposes. In contrast, silyl enol ether **306** was found to be stable enough to isolate (using Et_3N and water to quench the reaction mixture) and could subsequently be treated with a fluoride source (HF buffered with pyridine) at -78 ºC to generate aldehyde **307**, which was found to be stable at low temperature. Aldehyde **307** was then treated, *in situ*, with allyl magnesium bromide to generate the desired IMDA precursor, **308**, as a *ca*. 1:1 mixture of diastereomers, in 13% yield. Despite efforts to improve this reaction sequence, a higher yield was never obtained.



Scheme 4.6: *Reagents and conditions* (i) a) **190**, (1.0 mole equiv.), *i*-PrMgCl (1.5 mole equiv.), THF, -30 to 0 ºC, 2 h; b) CuBr•SMe_2 (0.1 mole equiv.), HMPA (3.0 mole equiv.), TMSCl (3.0 mole equiv.), **305** (2.1 mole equiv), THF, -78 to 18 ºC, 16 h; (ii) HF-pyridine/pyridine (2.9 mole equiv.), THF, -78 ºC, 2 h; (iii) allyl magnesium bromide (5.0 mole equiv.), -78 to 0 ºC, 1.25 h.

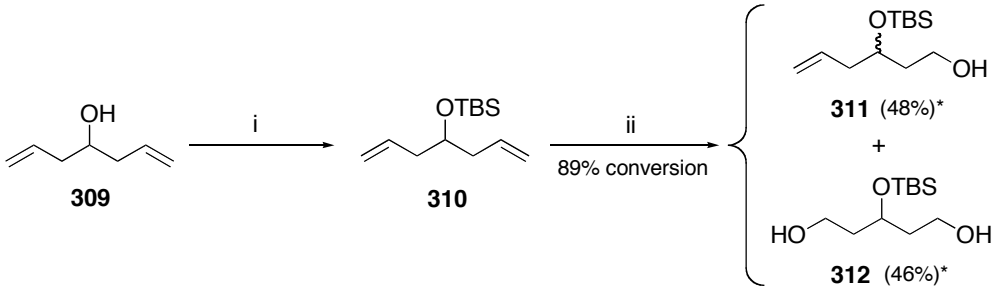
Although significant quantities of compound **308** could not be obtained, a small amount was used to evaluate whether this substrate would undergo the pivotal IMDA cycloaddition reaction. In the event, heating compound **308** in refluxing toluene for 16 h lead to a reaction mixture that appeared to contain the anticipated Diels-Alder adducts, as judged by ^1H NMR analysis. While these cycloadducts were not isolated or characterised, the feasibility of this approach had been confirmed and attention was now turned to the development an alternative, and higher yielding, synthetic route to the desired IMDA precursor.

4.4.1.1 Negishi cross-coupling approach

Despite the limited success of the Negishi cross-coupling reaction as described in the previous Chapter, the model study of this reaction had appeared extremely promising. It seemed probable, therefore, that the difficulties encountered earlier were a consequence of the instability of the alkyl iodide (dioxin) coupling partners. Thus, it was decided that the title reaction would be revisited as part of a new approach to the requisite IMDA precursor.

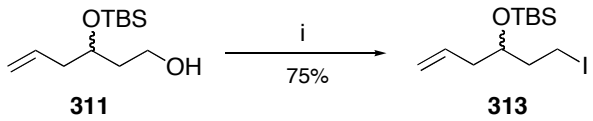
The synthesis of the desired coupling partner, *viz*. compound **313**, began with commercially available dienol **309**, which was converted, under standard conditions, into the corresponding and previously reported *tert*-butyldimethylsilyl (TBS) ether **310** (Scheme 4.7). The next stage involved conversion of this diene into alcohol **311** by selective ozonolysis.[185,186] One difficulty associated with a partial ozonolyses of this type is that the end point cannot readily be determined by classical methods, i.e. the appearance of blue colouration indicating excess ozone. Although dyes have been developed for the monitoring of selective reactions,[186] these rely on a significant difference in reactivity between the two (or more) olefinic bonds present in the molecule, an unlikely prospect in the case of diene **310**. In this instance, the yield of alcohol **311** was maximised by careful control of the reaction parameters (ozone flow rate, ozone content of the flow, reaction temperature, concentration) and optimization of the reaction time under these conditions. Using these conditions, a solution of 1 g of diene **310** in CH_2Cl_2/MeOH/2,6-lutidine[℘] was cooled to -78 ºC and treated with ozone for 10 mins. The ensuing mixture of ozonides was warmed to 0 ºC and granular $NaBH_4$ was added portionwise over 2 h. This procedure reliably afforded a chromatographically separable mixture of the staring material **310** (11% recovery), the unwanted diol **312** (46% at 89% conversion) and the required mono-ol **311** as a *ca*. 1:1 mixture of diastereomers (48% at 89% conversion).

℘ The presence of pyridine or 2,6-lutidine is known to slow the ozonolysis rate by slow oxidation to the corresponding *N*-oxide.[187] This can allow for small electronic differences in the olefins to impact the chemoselectivity of the reaction.[188]



Scheme 4.7: *Reagents and conditions* (i) 2,6-lutidine (1.75 mole equiv.), TBSOTf (1.5 mole equiv.), CH_2Cl_2, 0 to 18 ºC, 2.5 h; (ii) a) O_3, 2,6-lutidine (1.4 mole equiv.), CH_2Cl_2/MeOH, -78 ºC, 1 h; b) $NaBH_4$, MeOH, 0 to 18 ºC, 3 h. *Yields are over two steps and are based on recovered starting material.

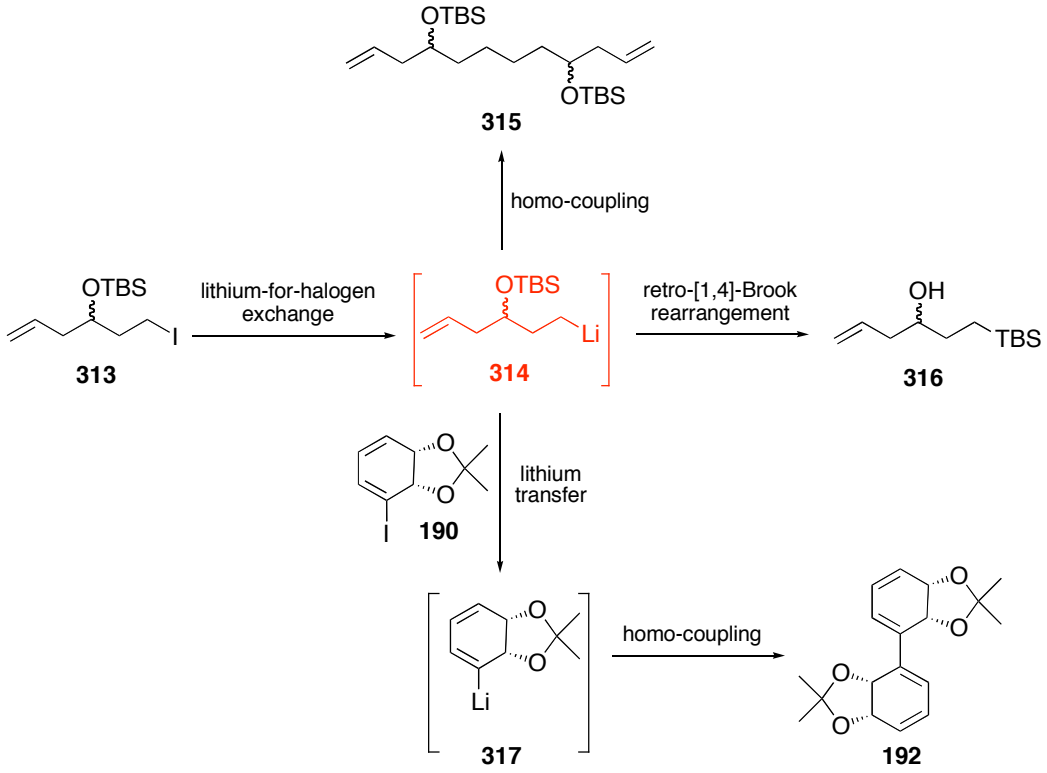
Alcohol **311** was readily converted into the corresponding iodide by treatment with molecular iodine in the presence of triphenylphosphine and imidazole (Scheme 4.8) to afford compound **313** in 75% yield.



Scheme 4.8: *Reagents and conditions* (i) PPh_3 (1.6 mole equiv.), imidazole (1.6 mole equiv.), I_2 (1.6 mole equiv.), benzene/Et_2O, 18 ºC, 2 h.

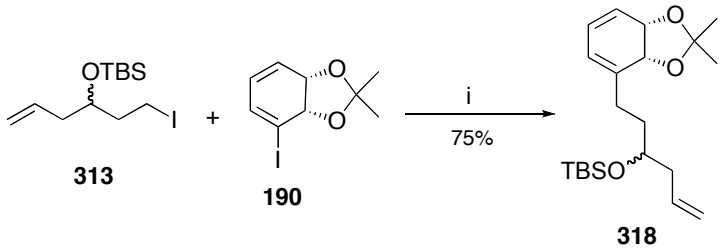
With the desired coupling partner in hand, initial attempts at the Negishi cross-coupling reaction were made using the protocol defined in Chapter Three. Specifically, a THF solution of iodide **313** was cooled to -78 ºC, then treated sequentially with *tert*-butyllithium (*t*-BuLi) and anhydrous zinc chloride (1.0 M solution in THF). The ensuing mixture was allowed warm to 18 ºC and acetonide **190** and Pd(PPh_3) were then added. Unfortunately, these conditions delivered a mixture of products. While one of these compounds was recognised as the desired coupled product, the others were identified as compounds **315, 316** and **192**[26] (Scheme 4.9). As demonstrated in Scheme 4.9 these products all derive from organolithium **314**, indicating that the desired lithium-zinc transmetallation reaction was not occurring efficiently. Further investigation revealed that when zinc chloride was used as the source of inorganic zinc then complete transmetallation required the use of ambient temperatures and extended reaction times. However, when zinc iodide was used, the corresponding organozinc reagent was formed at -78 ºC in less that 10 min. In addition, the formation of compound **316**, *via* a retro-Brook

rearrangement[189] of organolithium **314**, could be minimised by using Et_2O instead of THF as the reaction solvent. It has previously been shown that silyl group migrations of this type are highly solvent dependant. So, while these processes occur readily in THF and HMPA, they are suppressed in Et_2O.[189]



Scheme 4.9: *Alternative reaction pathways of organolithium **314**.*

Successful formation of the required organozinc reagent (involving treatment of a Et_2O solution of iodide **313** with *t*-BuLi then anhydrous zinc iodide) was followed by a Negishi cross-coupling of this species with acetonide **190**, in the presence of $Pd(Ph_3P)_4$, to afford compound **318** in 75% yield and as a *ca*. 1:1 mixture of diastereoisomers (Scheme 4.10).



Scheme 4.10: *Reagents and conditions* (i) a) **313** (1.0 mole equiv.), *t*-BuLi (2.2 mole equiv.), ZnI_2 (1.1 mole equiv.), Et_2O, -78 to 0 ºC, 1.25 h; b) **190** (1.0 mole equiv.), $Pd(PPh_3)_4$ (10 mol%), THF, 18 ºC, 3 h.

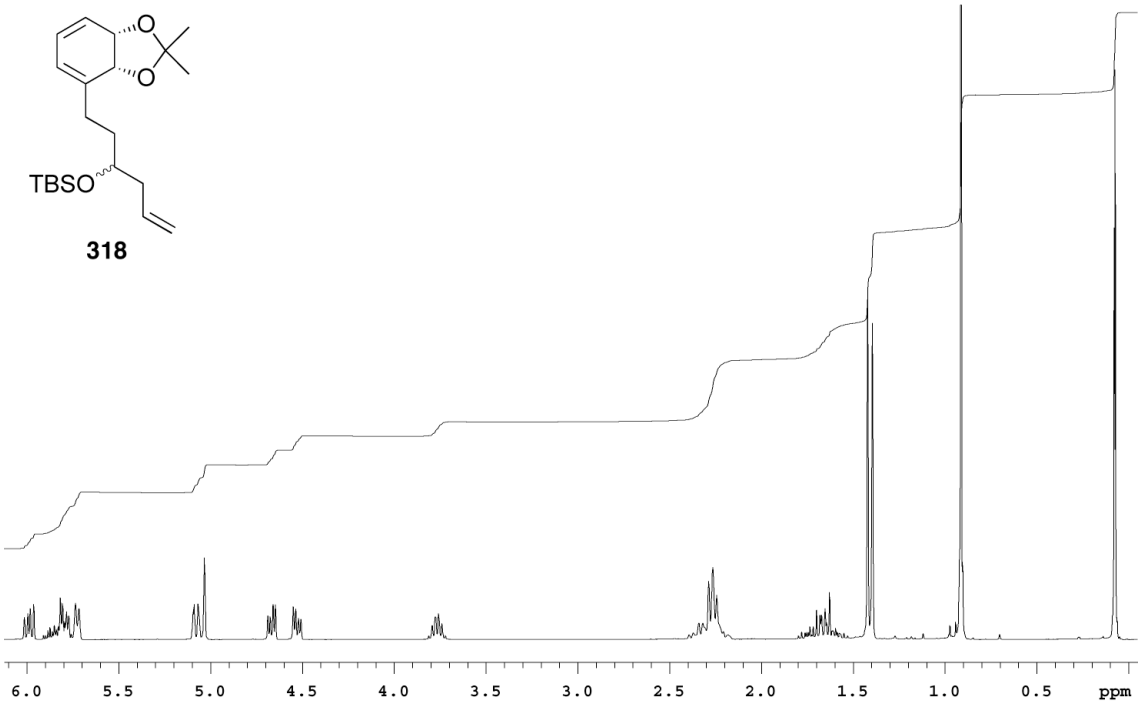


Figure 4.2*: 300 MHz ^{1}H NMR spectrum of triene* ***318*** *(*ca*. 1:1 mixture of diastereomers) (recorded in $CDCl_3$).*

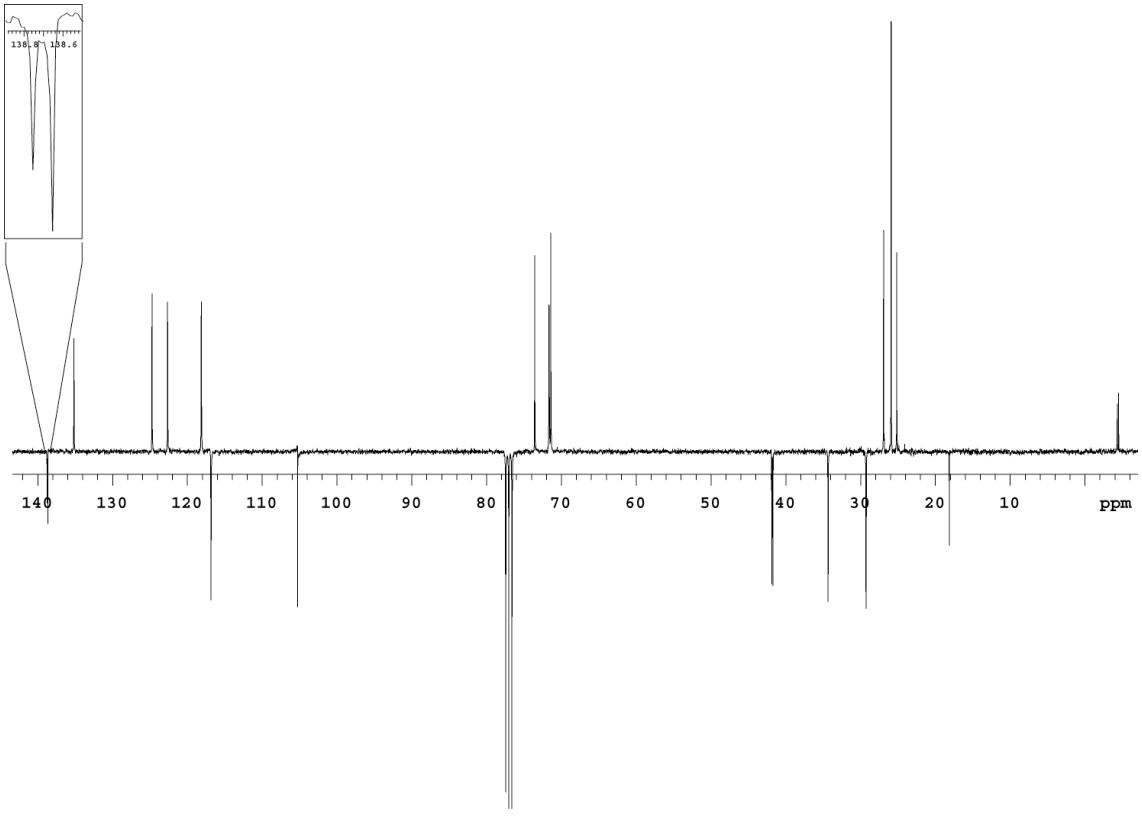
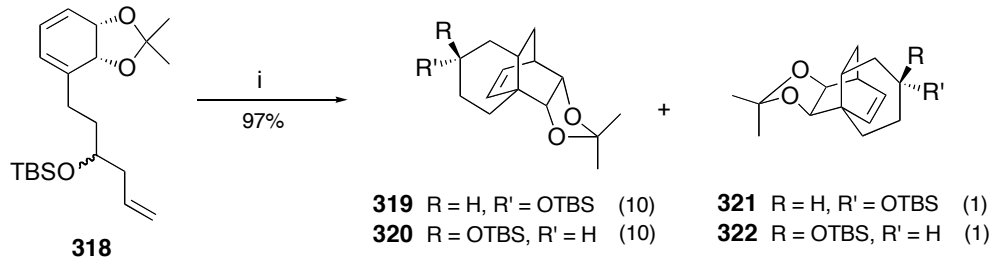


Figure 4.3: *75 MHz APT ^{13}C NMR spectrum of triene* ***318*** *(*ca*. 1:1 mixture of diastereomers) (recorded in $CDCl_3$).*

The spectral data obtained on triene **318** were indicative of a successful union of the two coupling partners. Thus, for example, the 300 MHz ^{1}H NMR spectrum (Figure 4.2) features six olefinic signals with three being attributable to the *c*-DHC moiety and three to the terminal alkene. Signals corresponding to the oxymethine protons were observed at δ 4.65 and 4.50, while the multiplets at δ 2.27 and 1.64 were assigned to the three methylene units. Although the ^{1}H NMR spectrum gave little indication that compound **318** was, in fact, a diastereomeric mixture, this is clearly evident by both GC mass spectrometry and analysis of the APT ^{13}C NMR spectrum (Figure 4.3). So, as expected, the APT ^{13}C NMR spectrum exhibits twenty-one distinct carbon resonances. However, on closer inspection many of these consist of two peaks, as demonstrated in the expanded region of Figure 4.3. The EI mass spectrum displays a molecular ion at *m/z* 364 and an accurate mass measurement on this species established that it was of the expected composition, *viz*. $C_{21}H_{36}O_3Si$.

4.4.2 The IMDA reaction and characterisation of cycloadducts 319 – 322

With the desired precursor now in hand, the pivotal IMDA reaction could be examined. The lack of activation of the dienophilic portion of substrate **318** meant that there was concern regarding whether or not an *endo*-selective cycloaddition reaction would be observed and whether the activation energy required to initiate such a process might be prohibitively high. In the event it was established that, by heating compound **318** in refluxing toluene for 16 h, a smooth cycloaddition reaction takes place generating a mixture of four cycloadducts, compounds **319 – 322** (Scheme 4.11), in a ratio of *ca*. 10:10:1:1, respectively, as determined by ^{1}H NMR analysis of the crude reaction mixture (Figure 4.4).



Scheme 4.11: *Reagents and conditions* (i) BHT (cat.), toluene, reflux, 16 h.

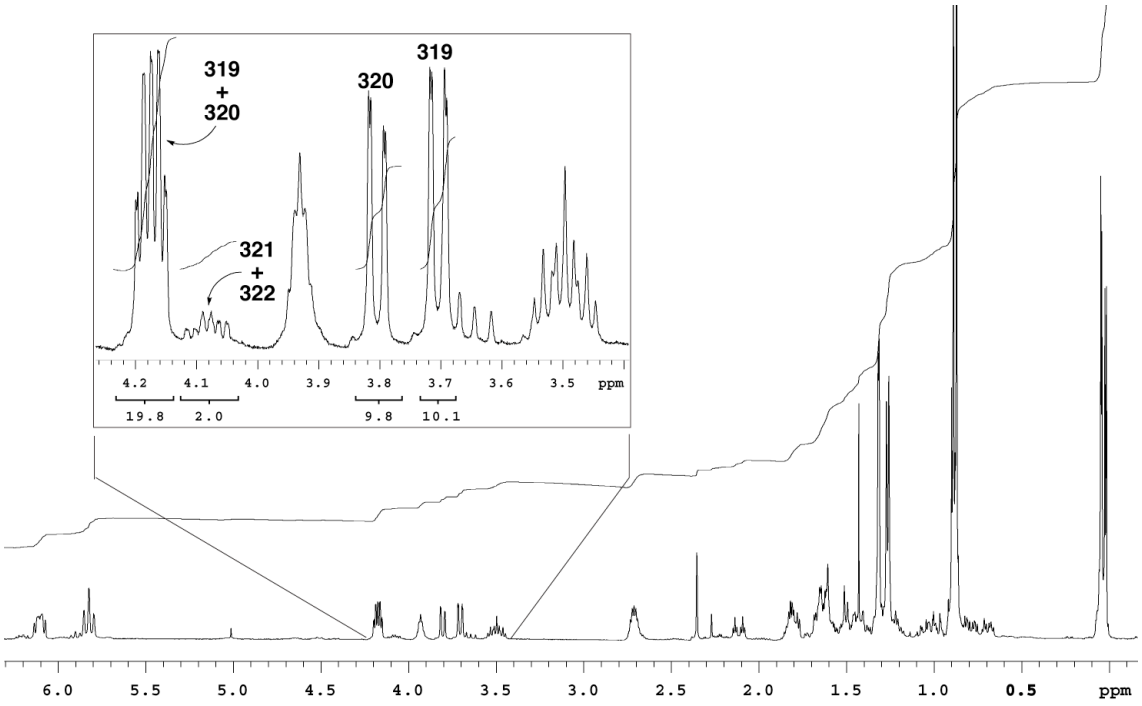
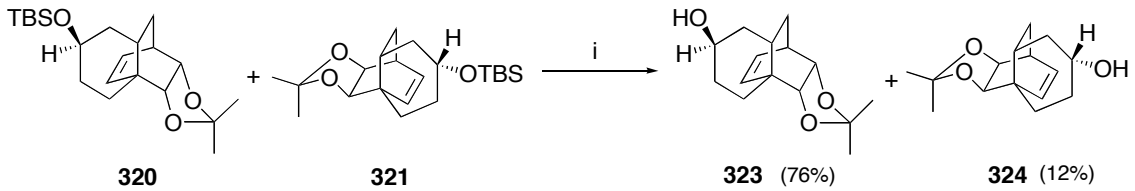


Figure 4.4: *300 MHz ^{1}H NMR spectrum of the crude reaction mixture of the IMDA reaction of triene* ***318*** *(recorded in $CDCl_3$).*

While column chromatography allowed for the isolation of clean samples of cycloadducts **319** and **322**, compounds **320** and **321** were obtained as an inseparable mixture. This mixture was thus subjected to TBAF-promoted deprotection of the silyl groups to afford the corresponding alcohols, **323** and **324**, which could now be readily separated from one another using conventional chromatographic techniques.



Scheme 4.12: *Reagents and conditions* (i) TBAF (2.3 mole equiv.), THF, 18 ºC, 72 h.

With all four cycloadducts separated, the assigned structures could be confirmed by single-crystal X-ray analysis. The X-ray structures clearly demonstrated that the major pair of cycloadducts, compounds **319** and **320** (Figure 4.5, Appendices 13 and 14), were formed *via* an *endo*-transition state and involved addition of the dienophile to the less hindered face of the diene, namely *via* an *anti*-addition pathway. These *endo*-, *anti*-adducts were obtained in 90%

combined yield and embody the required enantiomeric form of the tricyclic framework for the synthesis of (-)-platencin.

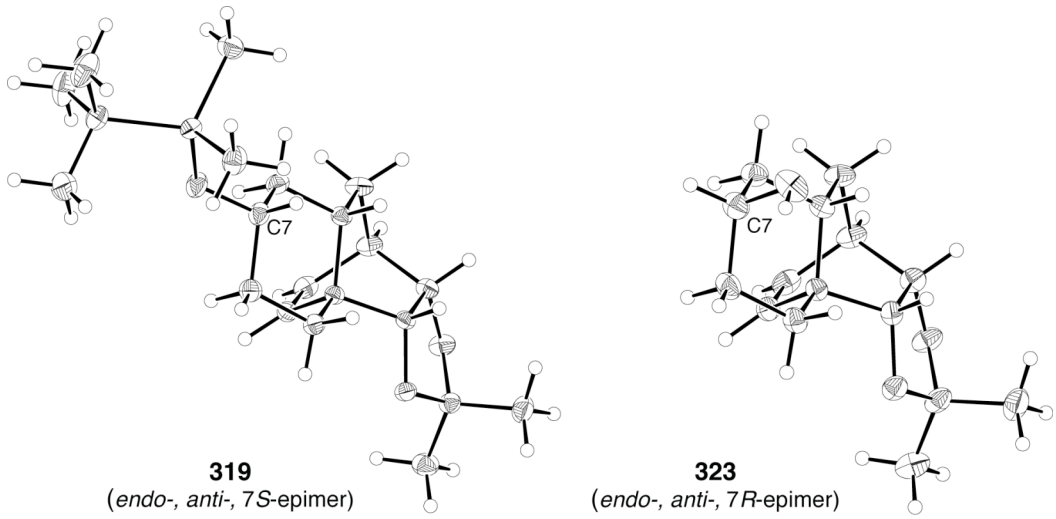


Figure 4.5: *Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of cycloadducts **319** and **323** (free-alcohol derivative of cycloadduct **320**).*

The minor pair of cycloadducts **321** and **322** (see Figure 4.6 for single-crystal X-ray structures of the corresponding free-alcohol derivatives **324** and **325**, respectively), were also formed *via* an *endo*-transition state. However, in these cases, addition of the dienophile had occurred at the sterically more crowded face of the diene to afford the corresponding *syn*-adducts. This pair of cycloadducts embody the opposite enantiomeric form of the tricyclic framework (see Section 1.4 "Enantiodivergent Syntheses") and so they could, in principle, be employed for the synthesis of *ent*-(+)-platencin. This may be a worthwhile endeavour since the non-natural enantiomer could also possess interesting biological properties. Accordingly, efforts to synthesise greater quantities of these compounds, *via* a *syn*-selective IMDA reaction, are described in the future work Section of this Chapter.

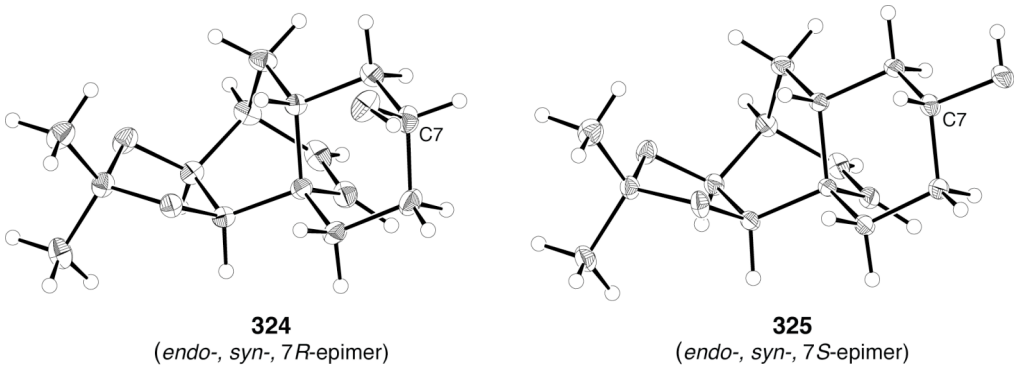
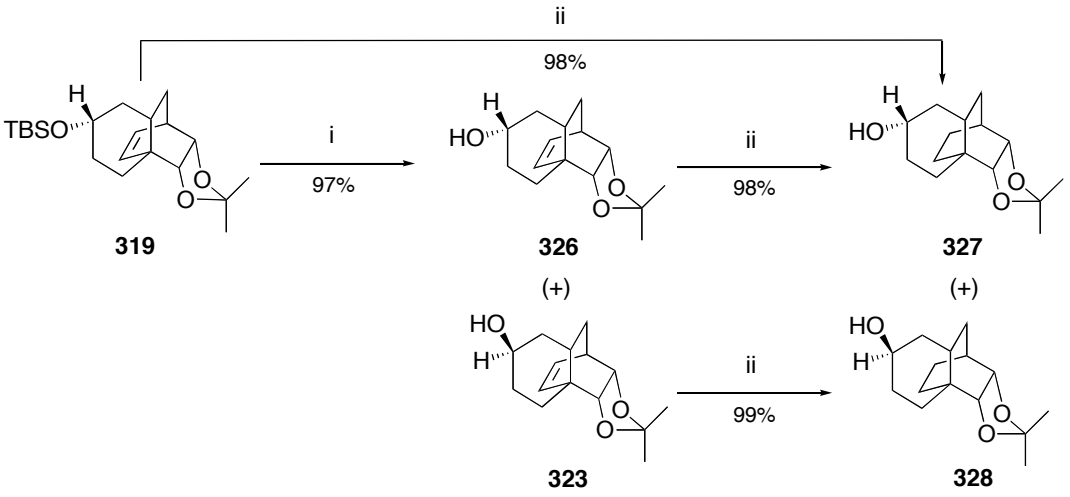


Figure 4.6: *Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of alcohols **324** and **325** (free-alcohol derivatives of cycloadducts **321** and **322**, respectively).*

The improved facial selectivity of this IMDA reaction, which involves a substrate possessing a six-carbon tether (10:1, *anti* : *syn*), when compared to the analogous five-membered example presented in Chapter Three (*ca.* 1:1, *anti* : *syn*) is noteworthy. This is most likely a consequence of the increased flexibility imparted to the system *via* lengthening the tether by one carbon.

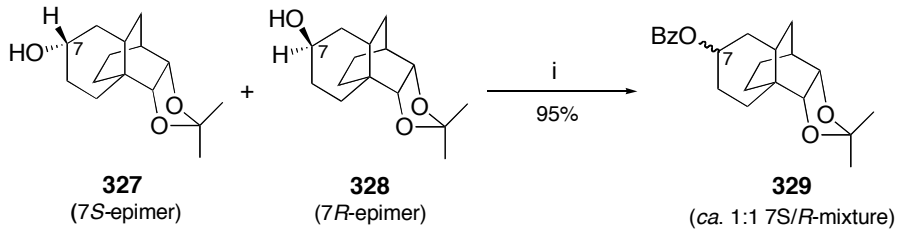
4.4.3 Elaboration of the IMDA products to the core structure of (-)-platencin

Having established the basic tricyclic framework of the target molecule through the acquisition of compounds **319** and **320**, attention now turned towards the elaboration of these materials into the core structure of (-)-platencin. As oxidation of the C7-hydroxyl group within these compounds was required to complete the synthesis of enone **91**, the stereochemistry at this centre was not important. Thus, it was decided that cycloadducts **319** and **320** would be combined and carried though the final parts of the reaction sequence as a mixture. While cycloadduct **319** was isolated as the TBS-ether derivate, cycloadduct **320** had been deprotected to the corresponding free-alcohol (**323**) in order to separate it from *syn*-adduct **321** (Scheme 4.12). Thus, TBS-ether **319** was treated with TBAF to afford the corresponding alcohol, before the product alcohols **323** and **326** were subject to hydrogenation, either independently, or as a mixture, at 1 atmosphere in the presence of 10% palladium on carbon. In this manner, the corresponding saturated systems **328** (99%, m.p. 131–132 °C) and **327** (98%, m.p. 120–121 °C) were obtained. Alternatively, it was found that if TBS-ether **319** was hydrogenated directly, the conditions employed for this reaction also resulted in deprotection of the TBS group to afford the corresponding saturated alcohol **327** in a single step.



Scheme 4.13: *Reagents and conditions* (i) TBAF (4.0 mole equiv.), THF, 18 ºC, 16 h; (ii) 10% Pd on C, H_2, EtOH, 18 ºC, 16 h.

Prior to hydrolysis of the acetonide residue, alcohols **327** and **328** were subjected (as a mixture) to *O*-benzoylation under standard conditions to provide ester **329** in 95% yield (Scheme 4.14). This protecting group was chosen on the basis that it would be able to withstand the acidic conditions required for removal of the acetonide group and could later be removed under sufficiently mild conditions to ensure the survival of sensitive functionalities associated with the target framework, particularly the exocyclic methylene unit.*



327 (7*S*-epimer) **328** (7*R*-epimer) **329** (*ca.* 1:1 7S/*R*-mixture)

Scheme 4.14: *Reagents and conditions* (i) Et_3N (4.0 mole equiv.), DMAP (4.0 mole equiv.), BzCl (2.9 mole equiv.), CH_2Cl_2, 0 ºC, 1 h.

The ^{1}H NMR spectrum of benzoate **329** (Figure 4.4) is consistent with the presence of a *ca*. 1:1 mixture of the C7 epimeric forms of this compound. While the aromatic and aliphatic proton resonances associated with each diastereomer overlap, creating complex mutiplets in these regions, the resonances associated with three oxymethine protons proved to be distinct to each isomer. In particular, the C7 proton appears as a singlet at δ 5.27 for 7*R*-**329** and as a triplet of triplets at δ 4.85 for 7*S*-**329**. Likewise, the doublet attributed to C9b-H is situated further downfield for 7*R*-**329** than 7*S*-**329**. The ^{13}C NMR spectrum displays the expected doubling of signals and is fully consistent with the assigned structure. Although the molecular ion was not observed in the EI mass spectrum, a strong peak at *m/z* 341 was attributed to a fragment ion resulting from loss of a methyl radical. An accurate mass measurement on this species confirmed the molecular formula of compound **329** as being $C_{22}H_{28}O_4$.

* A benzoate group could not have been used from the beginning of this synthesis, as it was incompatible with both the ozonolysis and the Negishi cross-coupling reactions.

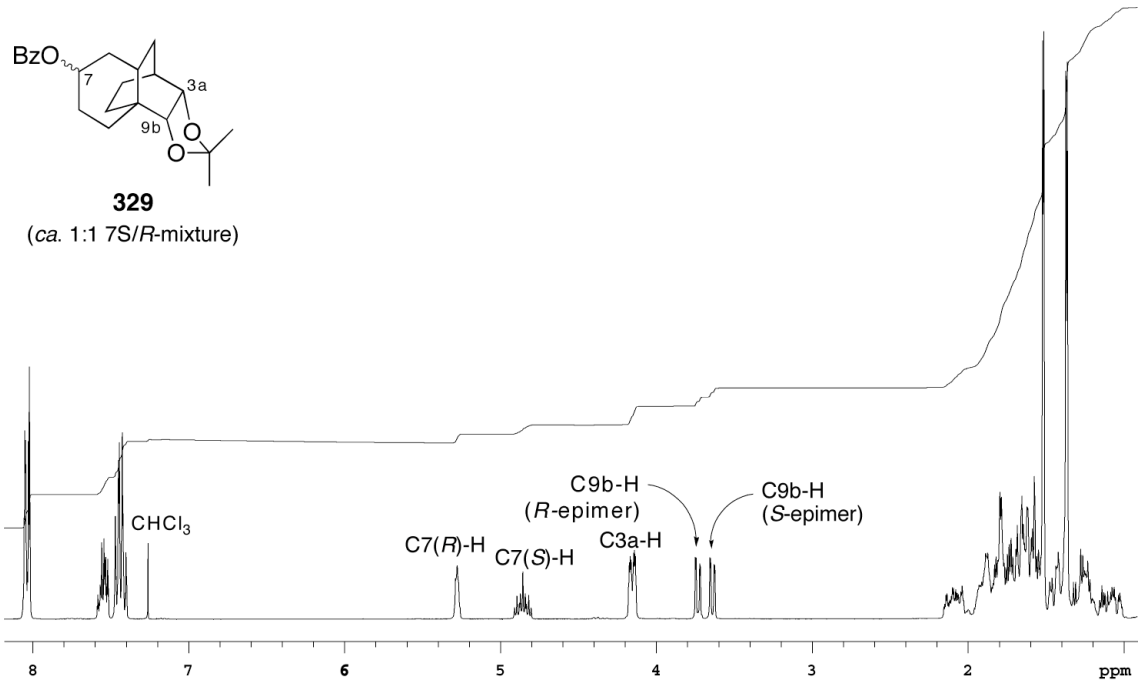


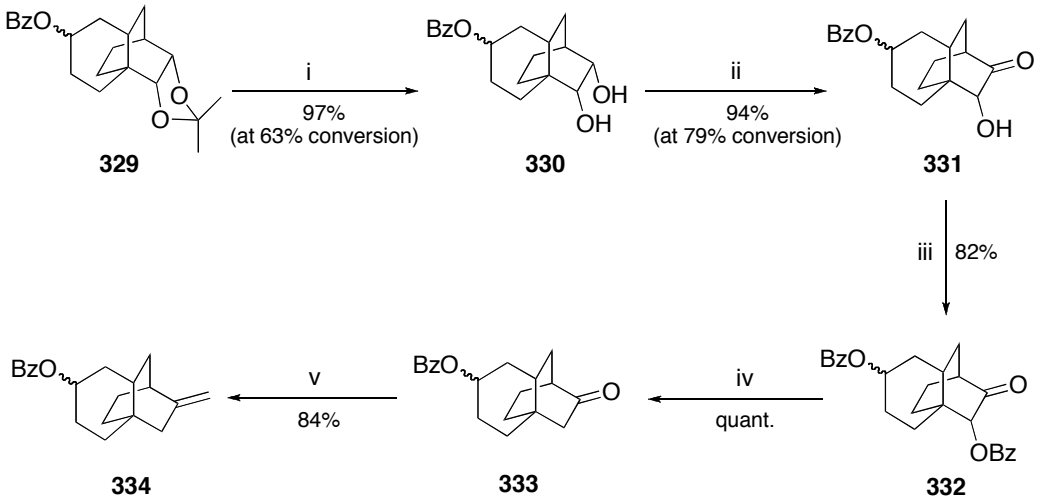
Figure 4.7: *300 MHz ^{1}H NMR spectrum of benzoate **329** (recorded in $CDCl_3$).*

The next stage of the synthesis focused on installation of the exocyclic methylene *via* manipulation of the diol moiety associated with compound **329** (Scheme 4.15). It was anticipated that this could be achieved by employing a similar series of functional group manipulations to that described in Chapter Two. Specifically, selective oxidation of the less hindered of the two hydroxyl moieties should afford the corresponding hydroxy-ketone possessing the carbonyl group in correct position to allow for introduction of the desired methylene unit *via* a Wittig methylenation reaction.

To this end, the acetonide residue of compound **329** was hydrolysed using previously defined conditions (acid-activated DOWEX-50 resin in aqueous MeOH at 110 °C for 48 h) to afford diol **330** (Scheme 4.15). Unfortunately, even under such forcing conditions complete conversion could not be achieved (63% conversion after 72 h). Initial attempts at selective oxidation of diol **330** using 4-acetamido-TEMPO (4-NHAc-TEMPO) and *p*-toluenesulfonic acid (*p*-TsOH•H_2O) afforded only low yields of hydroxy-ketone **331**, which was accompanied by an undesired by-product. However, it was found that side-reactions could be avoided by forming the active oxidising agent prior to addition to the reaction mixture, *via* premixing of *p*-TsOH•H_2O and 4-NHAc-TEMPO to form the corresponding oxoammonium salt, and by keeping the reaction at low temperature (0 ºC *c.f* 18 ºC). In this manner, acyloin **331** was obtained in 94% yield. The presence of prominent absorption bands at both 1714 and 3464 cm^{-1} in the IR spectrum of compound **331** confirmed the presence of both carbonyl and hydroxyl moieties in the molecule. The EI mass spectrum featured a molecular ion at *m/z* 314, consistent with a decrease of two mass units and the oxidative nature of the reaction. An accurate mass measurement on this ion

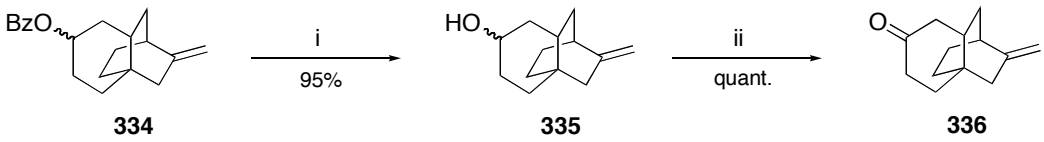
confirmed that it was of the anticipated composition, *viz.* $C_{19}H_{22}O_4$. Finally, the use of various connectivity and proximity experiments allowed full assignment of the ^1H and ^{13}C NMR spectra and it was thus established that the oxidation had occurred at the less hindered of the two hydroxy groups.

With acyloin **331** in hand, the free hydroxyl group was converted, using standard protocols, into the corresponding benzoate (**332**) (82%) in order to facilitate its removal *via* reductive cleavage. Thus, treatment of bis-benzoate **332** with SmI_2 in THF/MeOH at –78 °C resulted in a smooth reduction to the corresponding ketone **333** (quantitative yield), Wittig methylenation of which generated the corresponding olefin **334** in 84% yield (Scheme 4.15).



Scheme 4.15: Reagents and conditions (i) DOWEX-50 resin (acidic form), MeOH/H_2O (5:1), 110 °C, 72 h; (ii) 4-acetamido-TEMPO (2.2 mole equiv.), *p*-TsOH•H_2O (2.1 mole equiv.), CH_2Cl_2, 0 °C, 4 h; (iii) DMAP (4.0 mole equiv.), BzCl (3.0 mole equiv.), CH_2Cl_2, 0 ºC, 2 h; (iv) SmI_2 (2.2 mole equiv.), THF/MeOH (2:1), –78 °C, 15 min; (v) KHMDS (1.7 mole equiv.), Ph_3PCH_3Br (1.8 mole equiv.), THF, -78 to 18 ºC, 3.5 h.

With the exocyclic methylene in place all that remained to complete the synthesis of the core structure of (-)-platencin was to install the associated enone moiety. To this end, the ester group within compound **334** was saponified, using potassium carbonate in MeOH, to give alcohol **335**, which was then subjected to oxidation with IBX. At this point in the synthesis the two diastereomers converged to furnish a single, crystalline ketone, **336** (m.p. 57–59 °C), in 95% yield over the two steps (Scheme 4.16).



334 **335** **336**

Scheme 4.16: *Reagents and conditions* (i) K_2CO_3 (2.1 mole equiv.), MeOH, 18 ºC, 72 h; (ii) IBX (1.5 mole equiv.), DMSO, 18 ºC, 16 h.

The ^{1}H NMR spectrum of compound **336** features a complex aliphatic region and two signals in the olefinic region that were attributed to the protons of the terminal methylene unit. The ^{13}C NMR spectrum displays thirteen resonances, with the signal corresponding to the newly formed ketone carbon appearing at δ 211.7, and the peaks corresponding to two olefinic carbons visible at δ 150.8 and δ 105.5. The presence of a strong carbonyl absorption at 1713 cm^{-1} in the IR spectrum provided further evidence that the expected oxidation had taken place. A single-crystal X-ray structure was obtained (Figure 4.8, Appendix 17). This provided final confirmation of the assigned structure.

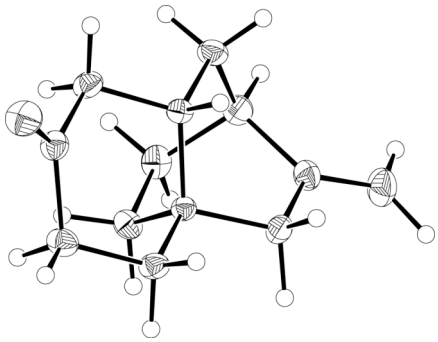
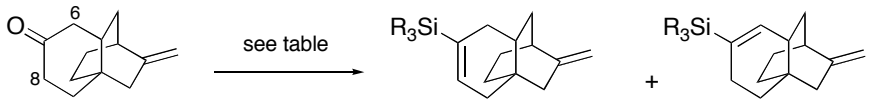


Figure 4.8: *Displacement Ellipsoid Plot (30%) derived from single-crystal X-ray analysis of ketone **336**.*

Completion of the synthesis of the target compound **91** required oxidation of precursor **336** to the corresponding enone. Initial attempts to introduce the carbonyl-conjugated olefin directly using IBX were unsuccessful. Thus, alternative protocols, which employed the corresponding silyl enol ether as an intermediate, were investigated. While it was hoped that deprotonation at C8 would be favoured under kinetic conditions, this was found not to be the case. Rather, a study of several bases and silylating agents (Table 4.2) showed little selectivity for the desired enol ether (**337**). As a result, it has, thus far, been impossible to avoid co-production of isomer **339**.

Table 4.1: *Formation of silyl enol ethers **337** and **338** using various bases and silylating agents.*



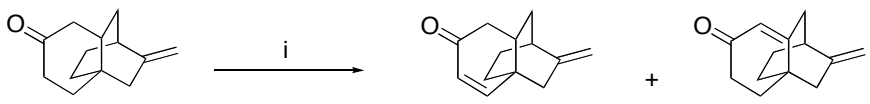
336 **337** **338**

R = TMS or TES

Entry	Reagents	Temperature	337* (desired)	338* (undesired)
1	LiHMDS, TESCl	-100 ºC and -78ºC	1	2
2	KHMDS, TESCl	-78 ºC	2	1
3	LiTMP, TESCl	-78 ºC	1	4
4	2,6-Lutidene, TMSOTf	0 to 18 ºC	1	1.4
5	Et_3N, TMSOTf	18 ºC	1	1.5
6	Me_3N, TMSOTf	0 ºC	4	1

*Ratios of **337** : **338** determined by GCMS or ^{1}H NMR analysis of the crude reaction mixture.

Under the optimal conditions identified to date (Table 4.1, Entry 6), which involved a protocol defined by Lalic and Corey in their synthesis of the core of platensimycin,[190] a solution of ketone **336** in CH_2Cl_2 was cooled to 0 °C then treated with trimethylamine and trimethylsilyl triflate (TMSOTf). A DMSO solution of the resulting mixture of silyl enol ethers was treated, at 18 °C, with IBX and 4-methoxypyridine-*N*-oxide (MPO). In this way a chromatographically separable mixture of compounds **91** (64%) and **339** (21%) was obtained.



336 **91** (64%) **339** (21%)

Scheme 4.17: *Reagents and conditions* (i) a) Me_3N, TMSOTf, CH_2Cl_2, 0 to 18 ºC, 2 h; b) IBX, MPO, DMSO, 18 ºC, 16 h.

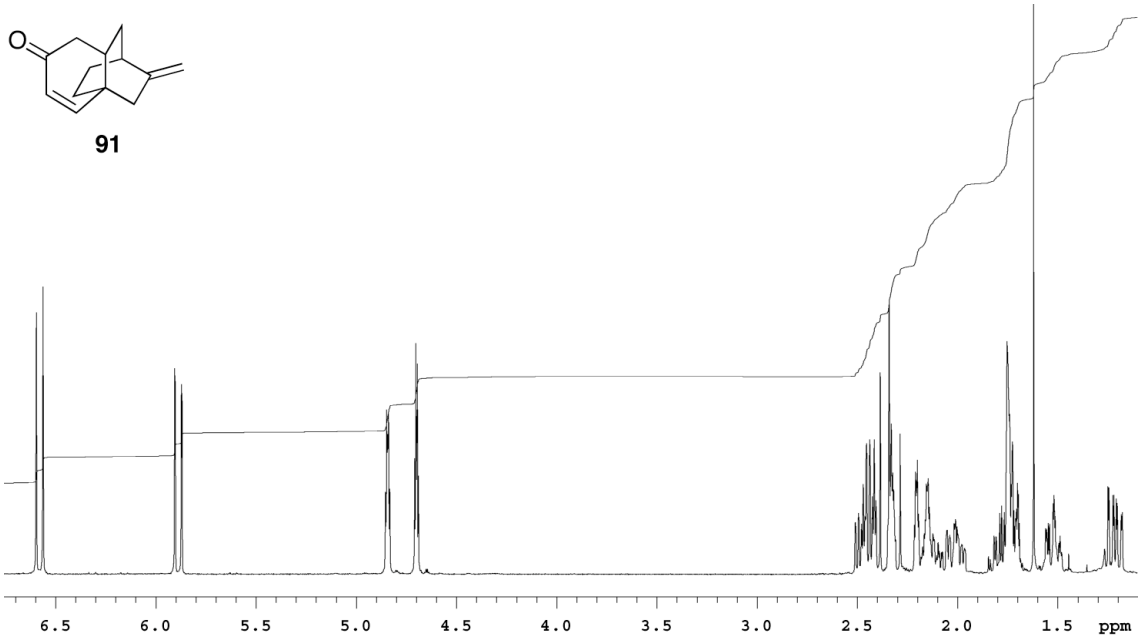


Figure 4.9: *300 MHz ^{1}H NMR spectrum of enone **91** (recorded in $CDCl_3$).*

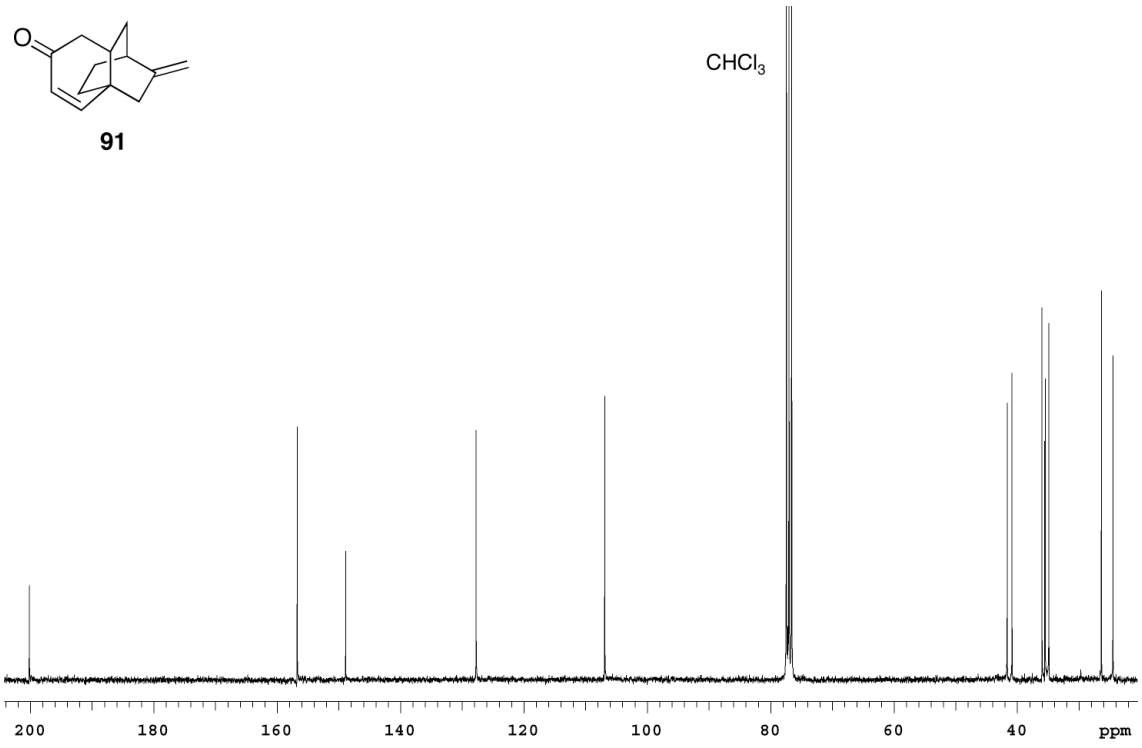


Figure 4.10: *300 MHz ^{13}C NMR spectrum of enone **91** (recorded in $CDCl_3$).*

The spectral data derived from each of these compounds were in full accord with the assigned structures. Furthermore, the ^{1}H NMR (Figure 4.9) and the ^{13}C NMR (Figure 4.10) spectra obtained on enone **91** completely matched the data reported by Nicolaou *et al*. Additionally, the

specific rotation obtained for compound **91** of +27 (*c* 0.9, $CHCl_3$), which is somewhat higher than the value reported by Nicolaou *et al*. [+6.3 (*c* 0.46, $CHCl_3$)], is in good agreement with the value of +27.5 (*c* 0.83, $CHCl_3$) recorded by Multzer *et al*. for the same compound.

The acquisition of enone **91** by the means described here constitutes a formal total synthesis of platencin owing to the recent reports from the Nicoloau and Rawal groups describing the conversion of compound **91** into the target **92**, as discussed in Section 4.2.

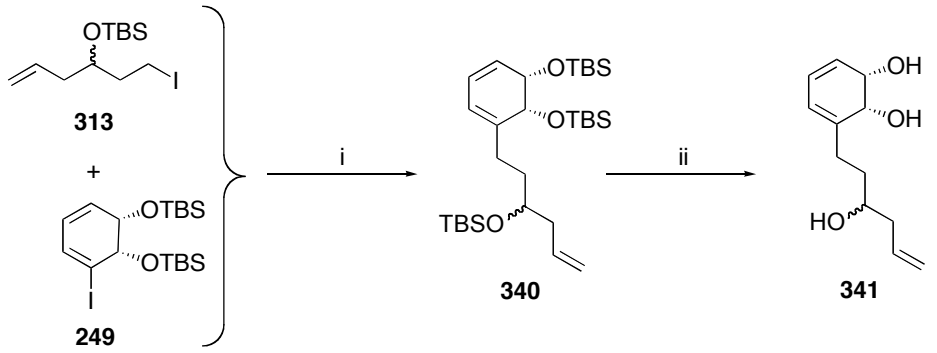
4.5 Future Research

The approach to (-)-platencin detailed in this Chapter represents a viable route to novel platencin analogues and future aspects of this project will be directed towards such ends. However, this research will be undertaken in collaboration with commercial partners and is therefore beyond the scope of this Thesis. Other future work will include establishing a synthesis of *ent*-(+)-platencin. The following Section discusses some preliminary results and proposes future strategies for achieving such ends.

4.6.1 Preliminary results

It was anticipated, at the outset of this work, that the unprotected *c*-DHC derivative **340**, would undergo a *syn*-selective IMDA cycloaddition reaction to afford the corresponding *endo*-, *syn*-cycloadducts as the major products. As discussed in Section 4.4.2 (page 123), such compounds (**324** and **325**, Figure 4.6) embody the non-natural enantiomeric form of the tricyclic framework. Accordingly, it was anticipated that they could be employed in a synthesis of *ent*-(+)-platencin. To this end, bis-ether **249** was subjected to a Negishi cross-coupling reaction with the organozinc reagent derived from alkyl iodide **313**, in the presence of $Pd(Ph_3P)_4$, to afford compound **340** in *ca*. 65% yield[#] and as a *ca*. 1:1 mixture of diastereoisomers (Scheme 4.18). Tris-silyl ether **340** was then deprotected using TBAF to afford triol **341**, the desired substrate for the IMDA reaction.

This compound was contaminated with the dimer derived from alkyl iodide **313** so an accurate yield could not be obtained.

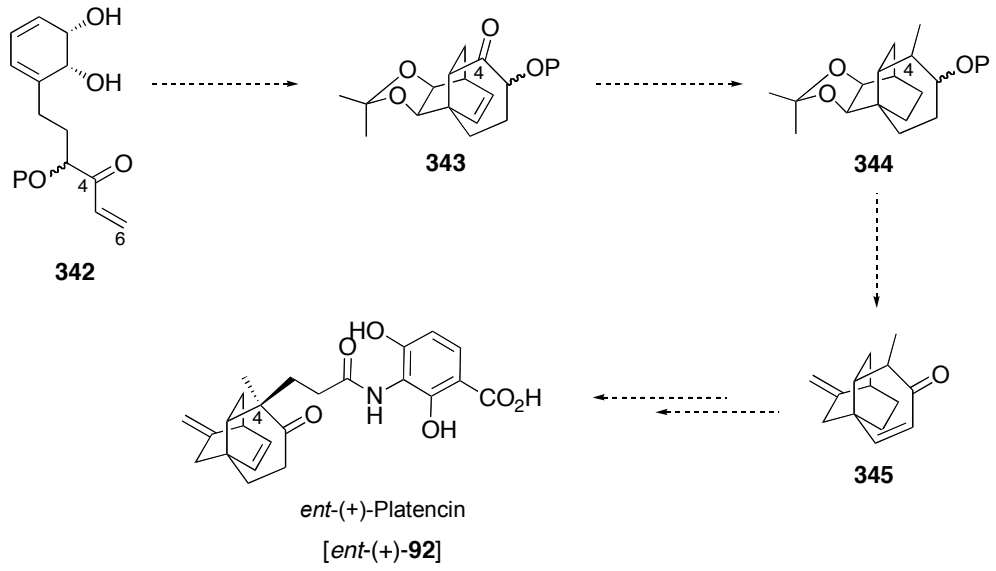


Scheme 4.18: *Reagents and conditions conditions* (i) a) **313** (1.0 mole equiv.), *t*-BuLi (2.2 mole equiv.), ZnI_2 (1.1 mole equiv.), Et_2O, -78 to 0 ºC, 1.25 h; b) **249** (1.0 mole equiv.), $Pd(PPh_3)_4$ (10 mol%), THF, 18 ºC, 3 h; (ii) TBAF, THF, 0 to 18 ºC, 2 h.

Unfortunately, despite several attempts, the IMDA cycloaddition reaction of triol **340** was unsuccessful. While no reaction was observed in refluxing toluene, temperatures higher than *ca.* 110 ºC were found to cause aromatisation of the *c*-DHC moiety. This result was not entirely unexpected as the parent diol is known to be a less reactive diene in Diels-Alder reactions[191] and much more susceptible to aromatisation than the corresponding acetonide-protected derivative.

4.6.2 Revised strategy

Based on the results presented above, it appears that the dienophile requires activation in order for the desired IMDA reaction to occur. Scheme 4.19 presents a revised approach to *ent*-(+)-platencin in which the IMDA substrate possesses a carbonyl group at C4 to increase the reactivity of the dienophile. In addition, it is envisioned that this carbonyl group could be used to install the C4 methyl group, the presence of which may also improve the selectivity of the final oxidation step, a matter that proved problematic in the initial synthesis.



Scheme 4.19: *Proposed approach to* ent-*(+)-platencin.*

Thus, it is anticipated that triene **342** will engage in an IMDA cycloaddition reaction to afford the *endo*-, *syn*-adduct **343** as the major product. Wittig methylenation, followed by reduction of both the newly installed exocyclic double bond and the internal olefin should afford compound **344**. It is envisioned that this compound could be elaborated, using procedures essentially identical to those detailed in this Chapter, to enone **345** and the propionamide-aniline unit then installed using protocols analogous to those employed in the Rawal[49] and Nicolaou[48] syntheses of (-)-platencin.

4.7 Conclusions

In the work described in this Chapter, *c*-DHC **88** has been converted, over 16 steps and in 9% overall yield, into the core structure of (-)-platencin. This synthesis, although longer than others, such as that of Mulzer *et al*,[178] has several desirable attributes:

(i) By virtue of the highly enantioselective enzymatic process used to produce the *c*-DHC starting material, this synthesis produces a product of higher enantiomeric purity (>99% ee) than other syntheses. The enantiomeric excesses associated with the other synthetic routes are limited either by the starting material (the commercially available (-)-perillaldehyde **292** used by Mulzer *et al.*,[178] Rutjes *et al.*,[179] and Lee *et al.*[177] is available in *ca.* >92% ee), or the asymmetric catalytic techniques used (Nicolau *et al*.[48] and Chen *et al*.[180] achieved 93% and 90%

ee, respectively). These days, an enantiomeric excess of 98% is generally considered the minimum acceptable level for chiral pharmaceutical reagents.[192]

(ii) Despite the promising antibacterial activity displayed by (-)-platencin, its use as a pharmaceutical agent is limited by its poor activity *in vivo*. Thus, synthesis of novel (-)-platencin analogues will be necessary in order to improve the pharmacokinetic properties. Therefore, rapid access to the core framework, which is likely to be a necessary part of all analogues, is desirable. While many of the published synthetic routes to (-)-platencin involve synthesis of the core *via* a bicyclic intermediate, the approach described in this Chapter employs a highly efficient and stereoselective IMDA cycloaddition reaction to synthesise the entire tricyclic framework in a single step. As such, it is anticipated that the present route may be well suited to the synthesis of platencin analogues.

(iii) The IMDA cycloaddition reaction employed in this synthesis not only produces the *anti*-addition products, which are of the correct enantiomeric form to allow the synthesis of (-)-platencin, but also affords the corresponding *syn*-adducts. These *syn*-cycloadducts embody the opposite enantiomeric form of the tricyclic framework and so, in principle, could be elaborated, using protocols essentially identical to those detailed in this Chapter, to *ent*-(+)-platencin. The synthesis and biological testing of this unnatural enantiomer could further aid the development of new antibacterial agents based on platencin.

Table 4.2: *Comparison of number of steps, overall yield and enantiomeric excesses (ee) of the various published routes to the core structure of platencin (compound **91**).*

Date Published	Group	No. of steps	Yield (%)	ee (%)	Reference
07/01/08	Nicoloau *et al.*	15	6	93	48
02/05/08	Rawal *et al.*	10	5	(±)	49
11/06/08	Lee et al.	15	10	>92	177
04/07/08	Mulzer *et al.*	5	26	>92	178
29/07/08	Rutjes *et al.*	9	16	>92	179
30/07/08	Chen et al.	13	9	90✦	180
18/09/08	Banwell *et al.*	16	9	>99	181

✦ Further enantiomeric enrichement can be achieved *via* a kinetic resolution followed by recrystallisation to afford essentially enantiomerically pure material (as determined by the observed optical rotation).[180]

In summary, the work presented in this Chapter provides a clear demonstration of the utility of the methodology developed and described in Chapter Three. By performing an IMDA cycloaddition reaction on an enantiopure *c*-DHC derivative, a formal total synthesis of the medicinally important antibacterial agent (-)-platencin has been achieved and in a manner that could provide an efficient synthetic route to the (-)-platencin analogues pertinent to the development of a medicinally useful compound.

CHAPTER FIVE

Experimental Procedures Associated with Work Described in Chapters Two to Four

5.1 General Procedures

Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied or, occasionally, recrystallised or distilled. Inorganic salts were purchased from Sigma Aldrich, AJAX, BDH or Unilab Chemical companies. The *cis*-1,2-dihydrocatechols used as starting materials were purchased from Professor Derek Boyd of The Queen's University of Belfast (Belfast, UK).

Tetrahydrofuran (THF), diethyl ether (Et_2O) and benzene were distilled, under nitrogen, from sodium benzophenone ketyl. Toluene was distilled, through a Vigreux column, from molten sodium metal. Methanol (MeOH) and ethanol (EtOH) were distilled from their respective magnesium alkoxide salts. Dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) were distilled under nitrogen, through Vigreux columns, from calcium hydride. *N,N*-Dimethylformamide (DMF), pyridine, triethylamine and di*iso*propylamine were stored over anhydrous 4Å molecular sieves that had previously been dried using a conventional microwave oven, then cooled under high vacuum and stored under anhydrous nitrogen or argon.

Glassware was soaked in a base bath (Pyroneg® in water) before being rinsed with water then acetone and oven-dried at 120 ºC. Assembled apparatus was evacuated (<0.1 mm Hg) and flushed three times with dry nitrogen, prior to use. All reaction mixtures were manipulated under nitrogen using standard Schlenk techniques and, unless otherwise specified, stirred magnetically. Deoxygenated solutions were obtained by bubbling nitrogen through the relevant solution for at least 15 min.

Ambient temperature was assumed to be *ca*. 18 ºC. Temperatures higher than ambient were attained using thermostated oil baths. To attain temperatures lower than ambient, a cooled, water circulating bath (0 to 10 ºC) or relevant cryostats (ice/water, 0 ºC; dry-ice/acetone, -78 ºC; liquid nitrogen/MeOH, -100 ºC) were used.

Organic solutions (extracts) obtained from the work-up of reaction mixtures were dried with sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) before filtration and concentration under reduced pressure on a rotary evaporator with the water bath temperature generally not exceeding 40 °C unless otherwise specified.

High pressure-promoted reactions were performed using a PISKA Pressure Systems Ltd. 20 kbar High Pressure Reactor. Reaction mixures were prepared (as solutions in CH_2Cl_2) in a compressible reaction vessel manufactured from Teflon® which was immersed in a castor oil/methanol mixture (85:15) contained in a cavity within the reactor and subjected to 19 kbar pressure at ambient temperature.

Ozonolyses were performed using a Model 500 Fischer portable ozone-generator with the luteinizing power and flow rate adjusted to 80 V and 50 L/h, respectively.

Flash column chromatography was performed using analytical grade solvents and silica gel 60 (230 – 400 mesh, 0.040 – 0.0063 mm) as supplied by Merck.

Analytical thin layer chromatography (tlc) was performed on self-indicating aluminium backed 0.2 mm thick silica gel 60 GF254 plates as supplied by Merck. Similarly, preparative layer chromatography (plc) was performed on self-indicating glass-backed 1.0 mm thick silica gel 60 GF254 plates, as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included: a) phosphomolybdic acid : cerium sulfate : sulfuric acid (conc.) : water (15 g : 2.5g : 15 mL : 485 mL); b) potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL); c) anisaldehyde : sulfuric acid (conc.) : ethanol (3ml : 4.5 mL : 200 mL); d) vanillin : ethanol : sulfuric acid (conc.) : water (18 g : 285 mL : 3 mL : 15 mL).

Melting points were measured on a Stanford Research Systems Optimelt – Automated Melting Point System or on a Reichert hot-stage microscope apparatus and are uncorrected.

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 20 °C in base-filtered deuterochloroform ($CDCl_3$) on a Varian Mercury 300 or Varian Inova 300 NMR spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In certain cases a Varian 500 spectrometer operating at 500 MHz for proton nuclei and 125 MHz for carbon nuclei and a Bruker 800 spectrometer operating at 800 MHz for proton nuclei were used. Signals arising from the residual protio-forms of the solvent were used as the internal standard. Chemical shifts are recorded as δ values in parts per million (ppm). ^1H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; qu = quintet, p =

pentet; m=multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet was used as the reference for proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra, the data are given as: chemical shift (δ), (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl. The assignment of signals observed in proton and carbon NMR spectra was assisted by conducting complementary connectivity and/or proximity experiments. Connectivity experiments used included the attached proton test (APT), homonuclear ($^1H/^1H$) correlation spectroscopy (COSY) and/or heteronuclear ($^1H/^{13}C$) correlation spectroscopy [heteronuclear multiple quantum coherence (HMQC) and/or heteronuclear multiple-bond correlation (HMQC)]. Proximity experiments included one or two-dimensional nuclear Overhauser effect and exchange spectroscopy (NOESY) experiments.

Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer. Samples were analysed as KBr discs (for solids) or as thin films on KBr plates (for liquids/oils).

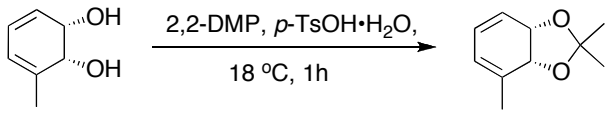
Mass spectrometry was performed by the Australian National University's Mass Spectrometric Services Unit located in the Research School of Chemistry, Canberra, Australia. Low and high resolution electron impact (EI) spectra were obtained on a VG Fisions AutoSpec M series three-sector (E/B/E) double-focussing mass spectrometer (located at the Australian National University). Low and high resolution electrospray (ES) mass spectra were recorded on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-MS or a VG Quattro II triple quadrupole MS instrument (both located at The Australian National University) operating in positive and/or negative ionisation mode. Gas chromatographic analysis and mass spectrometry (GCMS) were performed using, respectively, Varian 3400 Gas Chromatograph or an Agilent/HP 6890-5973 instrument (both located at The Australian National University) fitted with a capillary column. Peaks were detected using a flame ionisation detector operating at 300 ºC and helium was employed as the carrier gas (flow rate *ca*. 35 $cm.s^{-1}$) with an isothermal temperature programme of 50 ºC.

Optical rotations were measured between 17 to 20 °C with a Perkin-Elmer 241 polarimeter at the sodium-D line (λ = 589 nm) and the concentrations (*c*) (g/100 mL) indicated using spectroscopic grade chloroform ($CHCl_3$) as solvent. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations $[\alpha]_D$ were calculated using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and are given in $10^{-1}.deg.cm^2.g^{-1}$.

Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia, using a Carbo Erba EA 1106 CHN-O automatic elemental analyser.

5.2 Experimental Procedures for Chapter Two

(3a*R*,7a*S*)-2,2,4-Trimethyl-3a,7a-dihydro-1,3-benzodioxole (39)



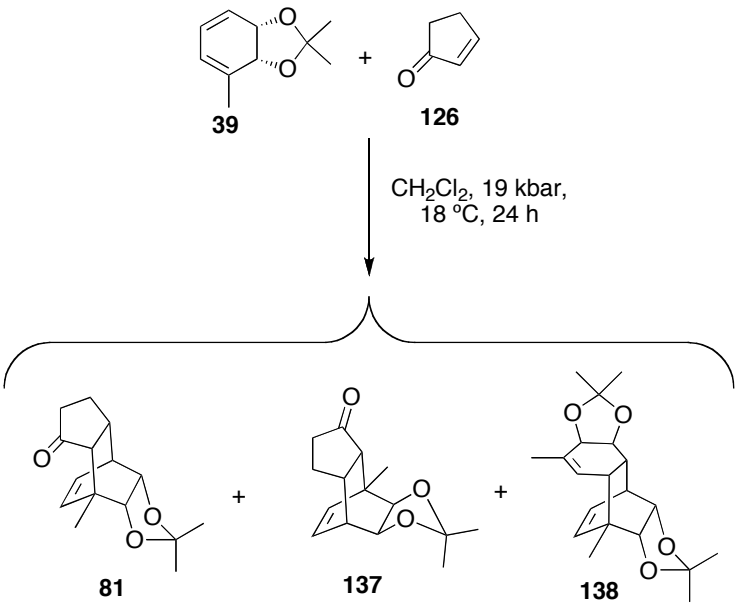
35 **39**

Following a procedure established by Banwell *et al.*[193] a solution of (1*S*,2*R*)-3-methylcyclohexa-3,5-diene-1,2-diol (**35**) (905 mg, 7.18 mmol) in 2,2-dimethoxypropane (150 mL) was treated with *p*-TsOH•H_2O (a few crystals) at 18 ºC and stirred at this temperature for 1 h. After this time, a further amount of *p*-TsOH•H_2O (14 mg, 0.072 mmol) was added and the ensuing mixture was stirred for 10 min then quenched by addition of $NaHCO_3$ (50 mL of a saturated aqueous solution) and diluted with CH_2Cl_2 (150 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were washed with NaOH (50 mL of a 2 M solution) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure (temp. = 30 ºC) to give title acetonide **39** (1.01 mg, 85%) as a pale brown oil (R_f = 0.6, 3:7 *v/v* EtOAc/hexane). This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 5.95 (dd, *J* = 9.6 and 5.6 Hz, 1H), 5.79 (dd, *J* = 9.6 and 4.0 Hz, 1H), 5.70 (m, 1H), 4.64 (dd, *J* = 8.7 and 4.0 Hz, 1H), 4.48 (d, *J* = 8.7 Hz, 1H), 1.87 (br s, 3H), 1.40 (s, 3H), 1.38 (s, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[193]

(3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-2,2,4-Trimethyloctahydro-5*H*-4,8-ethenoindeno[5,6-*d*][1,3]-dioxol-5-one (81), (3a*R*,4*R*,4a*R*,7a*R*,8*S*,8a*S*)-2,2,4-trimethyloctahydro-5*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxol-5-one (137) and (3a*R*,5a*R*,6*R*,6a*R*,9a*S*,10*S*,10a*S*,10b*S)*-2,2,4,6,8,8-hexamethyl-3a,5a,6,6a,9a10,10a,10b-octahydro-6,10-ethenonaphtho[1,2-*d*:6,7-*d*']bis[1,3]dioxole (138)



A solution of acetonide **39** (505 mg, 3.04 mmol) and cyclopentenone (**126**) (500 mL, 6.18 mmol) in CH_2Cl_2 (12 mL) was pressurized to 19 kbar in a PSIKA high-pressure reactor. After 24 h at *ca.* 18 °C the reaction mixture was removed from the reactor and concentrated under reduced pressure. The resulting dark-yellow oil was subjected to flash column chromatography (silica, 5:95 → 1:4 *v/v* EtOAc/hexane gradient elution) and thus affording two fractions, A and B.

Concentration of fraction A (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) gave a white solid, recrystallization (*iso*-propanol) of which afforded the *anti-isomer **81*** (549 mg, 73%) as white needles, m.p. = 79–80 °C.

^{1}H NMR (300 MHz) δ 6.12 (br t, *J* = 8.3 Hz, 1H), 5.77 (d, *J* = 8.3 Hz, 1H), 4.25 (ddd, *J* = 7.2, 3.3 and 0.9 Hz, 1H), 3.81 (dd, *J* = 7.2 and 1.3 Hz, 1H), 2.92 (m, 1H), 2.46 (m, 1H), 2.15–1.97 (complex m, 3H), 1.91 (d, *J* = 9.5 Hz, 1H), 1.68 (m, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (75 MHz) δ 219.7(C), 135.5 (CH), 129.8 (CH), 108.9 (C), 82.7 (CH), 78.9 (CH), 52.3 (CH), 41.9 (C), 40.7 (CH), 39.5 (CH_2), 36.3 (CH), 25.5 (CH_3), 25.1 (CH_2), 25.0 (CH_3), 18.7 (CH_3).

IR ν_{max} 2939, 2886, 1732, 1458, 1372, 1264, 1167, 1073, 1053, 889, 728 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 248 ($M^{+\bullet}$, 13%), 233 (69), 190 (89), 161 (82), 134 (85), 119 (81), 105 (89), 100 (87), 91 (83), 85 (86), 77 (59), 43 (100).

HREIMS Found: $M^{+\bullet}$, 248.1405. Calculated for $C_{15}H_{20}O_3$ requires $M^{+\bullet}$, 248.1412.

Elemental Analysis Found: C, 72.25; H, 8.21. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%.

Optical Rotation $[\alpha]_D$ = +172 (*c* 1.0, $CHCl_3$).

Concentration of fraction B (R_f = 0.4, 3:7 *v/v* EtOAc/hexane) afforded a yellow oil that was subjected to further flash column chromatography (silica, 0:1 → 1:9 *v/v* EtOAc/hexane gradient elution) and thus affording two fractions, C and D.

Concentration of fraction C [R_f = 0.4(1), 3:7 *v/v* EtOAc/hexane] afforded the *syn*-isomer **137** (99.5 mg, 13%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.17 (dd, *J* = 8.1 and 6.6 Hz, 1H), 5.84 (dd, *J* = 8.1 Hz, 1H), 4.07 (dd, *J* = 8.4 and 3.9 Hz, 1H), 3.69 (d, *J* = 8.1 Hz, 1H), 3.09 (m, 1H), 2.86 (m, 1H), 2.54 (d, *J* = 9.3 Hz, 1H), 2.15 -1.95 (m, 3H), 1.53 (m, 1H), 1.47 (s, 3H), 1.45 (s, 3H), 1.32 (s, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported by Banwell *et al*.[42]

Concentration of fraction D [R_f = 0.3(9), 3:7 *v/v* EtOAc/hexane] afforded *dimer* ***138*** (102 mg, 10%) as clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.90 (br t, *J* = 6.3 Hz, 1H), 5.65 (d, *J* = 8.1 Hz, 1H), 5.45 (m, 1H), 4.32 (ddd, *J* = 8.1, 5.4 and 0.9 Hz, 1H), 4.12 (dd, *J* = 5.1 and 1.5 Hz, 1H), 4.06 (br d, *J* = 5.1 Hz, 1H), 3.87 (dd, *J* = 7.2 and 2.2 Hz, 1H), 2.83 (m, 1H), 2.25 (br d, *J* = 9.0 Hz, 1H), 2.04 (m, 1H), 1.74 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (75 MHz) δ 137.1 (CH), 133.0 (C), 127.9 (CH), 122.4 (CH), 108.5 (C), 107.5 (C), 82.8 (CH), 79.2 (CH), 78.4 (CH), 73.6 (CH), 43.5 (C), 40.4 (CH), 39.0 (CH), 35.5 (CH), 27.9 (CH_3), 26.8 (CH_3), 25.5 (CH_3), 25.1 (CH_3), 19.6 (CH_3), 19.4 (CH_3).

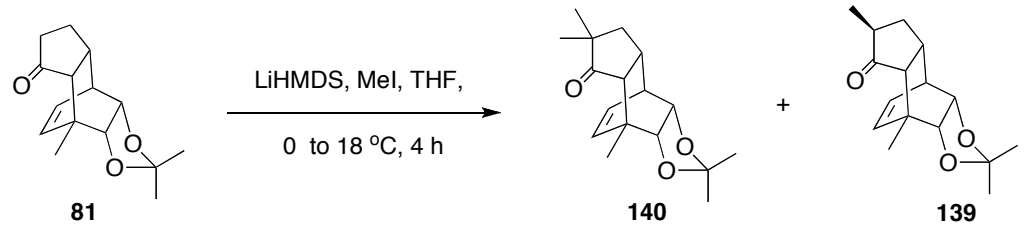
IR ν_{max} 2981, 2935, 2874, 1454, 1370, 1240, 1209, 1161, 1062, 1025, 882, 725 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 332 ($M^{+\bullet}$, 2%), 317 (10), 274 (14), 216 (52), 109 (81), 108 (100), 80 (53).

HREIMS Found: $M^{+\bullet}$, 332.1973. $C_{20}H_{28}O_4$ requires $M^{+\bullet}$, 332.1988.

Optical Rotation $[\alpha]_D$ = +57 (*c* 0.3, $CHCl_3$).

(3a*R*,4*R*,4a*R*,7a*R*,8*S*,8a*S*)-2,2,4,6,6-Pentamethyloctahydro-5*H*-4,8-ethenoindeno[5,6-*d*]-[1,3]dioxol-5-one (140) and (3a*R*,4*R*,4a*R*,6*S*,7a*R*,8*S*,8a*S*)-2,2,4,6-tetramethyloctahydro-5*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxol-5-one (139)



81 140 139

A solution of ketone **81** (2.00 g, 8.05 mmol) in THF (80 mL) was cooled to 0 °C then treated, dropwise, with LiHMDS (8.8 mL of a 1.0 M solution in THF, 8.80 mmol). The resulting mixture was maintained at 0 °C for 45 min then warmed to 18 °C over a period of 1.25 h. The reaction mixture was then re-cooled to 0 °C and treated, dropwise, with iodomethane (526 mL, 8.45 mmol). The ensuing mixture was stirred at 0 °C for 45 min then warmed to 18 °C over 1.25 h, quenched with NH_4Cl (20 mL of a saturated aqueous solution) then diluted with CH_2Cl_2 (80 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing orange semi-solid was subjected to flash column chromatography (silica, 5:95 → 15:85 *v/v* EtOAc/hexane gradient elution) and thus affording three fractions, A, B and C.

Concentration of fraction A (R_f = 0.4, 3:7 *v/v* EtOAc/hexane) afforded the *gem-dimethylated derivative **140*** (310 mg, 15% at 92% conversion) as white crystalline solid, m.p. = 101–105 °C.

^{1}H NMR (300 MHz) δ 5.95 (m, 1H), 5.82 (br d, *J* = 8.4 Hz, 1H), 5.27 (ddd, *J* = 7.2, 3.3 and 0.9 Hz, 1H), 3.81 (dd, *J* = 7.2 and 1.2 Hz, 1H), 2.86 (m, 1H), 2.48 (m, 1H), 2.14 (d, *J* = 1.5 Hz, 1H), 1.87 (dd, *J* = 12.9 and 8.9 Hz, 1H), 1.56 (s, 3H), 1.34 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (75 MHz) δ 221.3 (C), 135.9 (CH), 129.8 (CH), 109.0 (C), 83.2 (CH), 78.9 (CH), 49.6 (CH), 47.0 (C), 40.7 (C), 40.4 (CH_2), 39.4 (CH) 33.4 (CH), 26.4 (CH_3), 25.5 (CH_3), 25.0 (CH_3), 22.1 (CH_3), 18.7 (CH_3).

IR ν_{max} 2963, 2933, 2871, 1731, 1455, 1373, 1324, 1269, 1254, 1208, 1166, 1054, 1073, 891, 875, 820, 732 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 276 ($M^{+\bullet}$, 13%), 261 (38), 218 (90), 176 (78), 134 (80), 105 (100).

HREIMS Found: $M^{+\bullet}$, 276.1727. $C_{17}H_{24}O_3$ requires $M^{+\bullet}$, 276.1725.

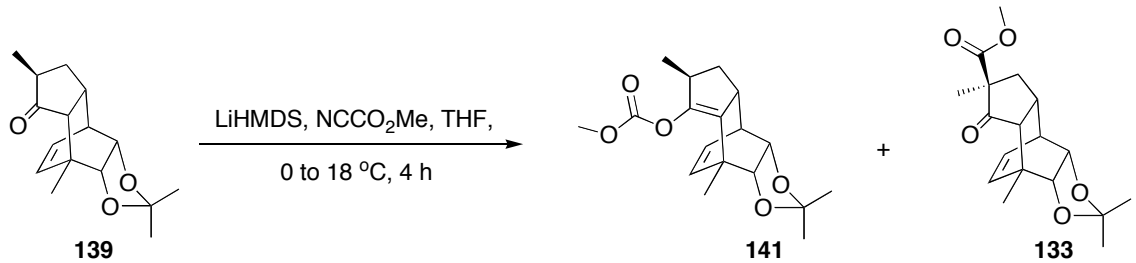
Optical Rotation $[\alpha]_D$ = +88 (*c* 1.0, $CHCl_3$).

Concentration of fraction B (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded the *title compound* ***139*** (1.58 g, 82% at 92% conversion) as a white crystalline solid, m.p. = 67–69 °C.

^{1}H NMR (300 MHz) δ 6.16 (br t, *J* = 8.3 Hz, 1H), 5.71 (d, *J* = 8.3 Hz, 1H), 4.26 (ddd, *J* = 7.8, 3.5 and 0.7 Hz, 1H), 3.83 (dd, *J* = 7.2 and 1.2 Hz, 1H), 2.93 (m, 1H), 2.31 (br t, *J* = 9.4 Hz, 1H), 2.13 (m, 1H), 1.95 (d, *J* = 9.3 Hz, 2H), 1.63 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (75 MHz) δ 219.5 (C), 134.9 (CH), 129.7 (CH), 108.2 (C), 82.2 (CH), 78.6 (CH), 52.4 (CH), 43.7 (CH), 41.8 (C), 40.4 (CH), 34.4 (CH), 33.2 (CH_2), 25.0 (CH_3), 24.6 (CH_3), 18.4 (CH_3), 13.8 (CH_3).
IR ν_{max} 2974, 2932, 2874, 1732, 1455, 1373, 1266, 1207, 1164, 1078, 1055, 886, 732 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 262 ($M^{+\bullet}$, 10%), 247 (43), 204 (86), 175 (57), 162 (72), 134 (100), 105 (96), 100 (82), 92 (60), 91 (63), 43 (69).
HREIMS Found: $M^{+\bullet}$, 262.1568. $C_{16}H_{22}O_3$ requires $M^{+\bullet}$, 262.1569.
Optical Rotation $[\alpha]_D$ = +172 (*c* 0.5, $CHCl_3$).

Concentration of fraction C [R_f = 0.2(5), 3:7 *v/v* EtOAc/hexane] afforded the starting ketone **81** (169 mg, 8% recovery) as a white crystalline solid. This material was identical, in all respects, with authentic material.

Methyl (3a*R*,4*R*,6*S*,7a*R*,8*S*,8a*S*)-2,2,4,6-tetramethyl-3a,6,7,7a,8,8a-hexahydro-4*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxol-5-yl carbonate (141) and methyl (3a*R*,4*R*,4a*R*,6*S*,7a*R*,8*S*,8a*S*)-2,2,4,6-tetramethyl-5-oxooctahydro-3a*H*-4,8-ethenoindeno-[5,6-*d*][1,3]dioxole-6-carboxylate (133)



139 **141** **133**

A solution of compound **139** (1.94 g, 7.41 mmol) in THF (75 mL) was cooled to 0 °C then treated, dropwise, with LiHMDS (8.9 mL of a 1.0 M solution in THF, 8.90 mmol). The resulting mixture was maintained at 0 °C for 45 min, warmed to 18 °C over 1.25 h then re-cooled to 0 °C and treated dropwise with Mander's reagent (1.18 mL, 14.9 mmol). Stirring was continued at 0 °C for 45 min then the reaction mixture was warmed to 18 °C over 1.25 h, quenched with NH_4Cl (20 mL of a saturated aqueous solution) and diluted with CH_2Cl_2 (80

mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases then washed with water (2 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash column chromatography (silica, 5:95 → 15:85 *v/v* EtOAc/hexane gradient elution) and thus affording two fractions, A and B.

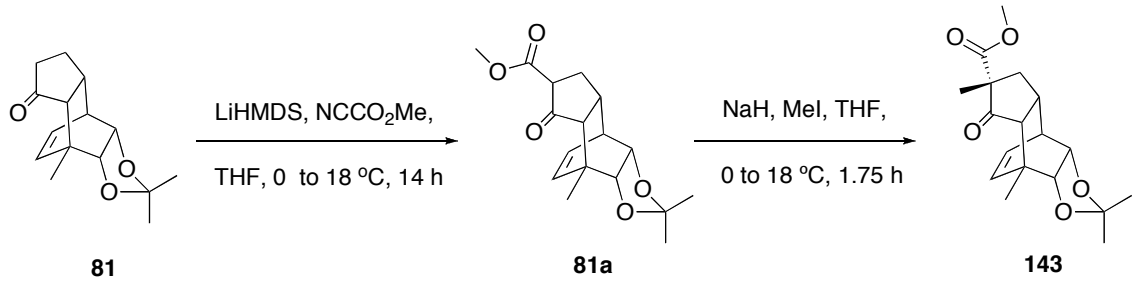
Concentration of fraction A (R_f = 0.5, 3:7 *v/v* EtOAc/hexane) afforded the *title enol carbonate* ***141*** (71 mg, 3%) as a white needles, m.p. = 100–104 °C.

^{1}H NMR (300 MHz) δ 5.97 (d, *J* = 8.1 Hz, 1H), 5.81 (dd, *J* = 8.1 and 6.8 Hz, 1H), 4.36 (dd, *J* = 7.2 and 3.6 Hz, 1H), 4.02 (br d, *J* = 6.8 Hz, 1H), 3.82 (s, 3H), 2.85 (m, 1H), 2.70 (m, 2H), 1.80–1.55 (complex m, 2H), 1.40 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (75 MHz) δ 153.8 (C), 145.5 (C), 138.0 (CH), 130.9 (C), 127.2 (CH), 109.5 (C), 80.6 (CH), 80.3 (CH), 55.2 (CH_3), 42.6 (C), 41.7 (CH), 40.1 (CH), 39.3 (CH), 37.7 (CH_2), 25.5 (CH_3), 25.0 (CH_3), 16.3(5) (CH_3), 16.3(2) (CH_3).
IR ν_{max} 2958, 2939, 2881, 1764, 1693, 1456, 1441, 1371, 1272, 1245, 1207, 1182, 1072, 1045, 1010, 950, 896, 871, 818, 783, 729 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 320 ($M^{+\bullet}$, 5%), 305 (4), 247 (51), 203 (100), 187 (69), 186 (95), 161 (60), 144 (92), 101 (77).
HREIMS Found: $M^{+\bullet}$, 320.1631. $C_{18}H_{24}O_5$ requires $M^{+\bullet}$, 320.1624.
Optical Rotation $[\alpha]_D$ = +50 (*c* 0.9, $CHCl_3$).

Concentration of fraction B (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded a solid that was recrystallized (EtOAc) to give *title keto-ester* ***133*** (2.09 g, 88%) as white needles, m.p. = 91–94 °C.

^{1}H NMR (300 MHz) δ 5.97 (br t, *J* = ca. 5.0 Hz, 1H), 5.84 (d, *J* = 5.0 Hz, 1H), 4.28 (dd, *J* = 4.2 and 2.1 Hz, 1H), 3.82 (d, *J* = 4.2 Hz, 1H), 3.66 (s, 3H), 2.88 (m, 1H), 2.57 (m, 2H), 2.26 (d, *J* = 6.0 Hz, 1H), 1.57 (s, 3H), 1.34 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H).
^{13}C NMR (75 MHz) δ 213.2 (C), 173.0 (C), 136.5 (CH), 130.0 (CH), 109.6 (C), 83.3 (CH), 79.1 (CH), 58.4 (C), 52.9 (CH_3), 51.8 (CH), 41.3 (C), 39.7 (CH), 38.2 (CH_2), 34.8 (CH), 25.8 (CH_3), 25.3 (CH_3), 18.9 (CH_3), 18.8 (CH_3).
IR ν_{max} 2976, 2935, 2878, 1753, 1728, 1456, 1375, 1267, 1208, 1151, 1069, 889, 736 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 320 ($M^{+\bullet}$, 18%), 305 (60), 262 (89), 247 (74), 202 (78), 173 (55), 157 (59), 134 (78), 105 (84), 100 (100), 92 (62), 91 (66), 85 (59), 69 (52), 43 (71), 41 (58).
HREIMS Found: $M^{+\bullet}$, 320.1621. $C_{18}H_{24}O_5$ requires $M^{+\bullet}$, 320.1624.
Optical Rotation $[\alpha]_D$ = +105 (*c* 1.0, $CHCl_3$).

Methyl (3a*R*,4*R*,4a*R*,7a*R*,8*S*,8a*S*)-2,2,4-trimethyl-5-oxooctahydro-3a*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxole-6-carboxylate (143a) methyl (3a*R*,4*R*,4a*R*,6*R*,7a*R*,8*S*,8a*S*)-2,2,4,6-tetramethyl-5-oxooctahydro-3a*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxole-6-carboxylate (143)



81 **81a** **143**

Step i: A solution of ketone **81** (202 mg, 0.82 mmol) in THF (2.5 mL) was cooled to −78 °C then treated, dropwise over 30 min, with LiHMDS (1.22 mL of 1.0 M solution in THF, 1.22 mmol). The ensuing mixture was stirred at −78 °C for 1.5 h then treated with Mander's reagent (71 mL, 0.90 mmol) before being allowed to warm to 18 °C over 14 h. The reaction mixture was then treated with water (5 mL) and CH_2Cl_2 (5 mL) and the separated aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic fractions were washed with $NaHCO_3$ (2 mL of a saturated aqueous solution) and brine (2 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 → 1:3 *v/v* EtOAc/hexane gradient elution) and concentration of the relevant fractions gave a light-yellow oil tentatively identified as a mixture of *title compound **81a*** (stereochemistry not determined) and its various tautomers (191 mg, 78%) (R_f = 0.3, 3:7 *v/v* EtOAc/hexane). This material was subjected, without full characterization, to step ii of the reaction sequence as detailed immediately below.

Step ii: A suspension of NaH (15 mg, 0.63 mmol) in THF (5 mL) was cooled to 0 °C then treated with a sample of compound **81a** obtained in step i (94 mg, 0.31 mmol) dissolved in THF (1.5 mL). The ensuing mixture was warmed to 18 °C then allowed to stir at this temperature for 45 min before being treated with iodomethane (96 mL, 1.54 mmol). After a further 1 h, the reaction mixture was treated with NH_4Cl (5 mL of a saturated aqueous solution) and CH_2Cl_2 (5 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were washed with water (5 mL) and brine (5 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The white solid so obtained was subjected to flash column chromatography (silica, 1:9 → 3:7 *v/v* EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded the *title keto-ester **143*** (90 g, 91%) as white needles, m.p. = 92–96 °C.

^{1}H NMR (300 MHz) δ 6.01 (m, 1H), 5.76 (br d, *J* = 8.4 Hz, 1H), 4.27 (br dd, *J* = 7.5 and 4.8 Hz, 1H), 3.81 (dd, *J* = 7.5 and 1.2 Hz, 1H), 3.68 (s, 3H), 2.95 (m, 1H), 2.48 (m, 1H), 2.36 (dd, *J* = 13.5 and 7.2 Hz, 1H), 2.13 (d, *J* = 9.9 Hz, 1H), 1.92 (dd, *J* = 13.8 and 9.2 Hz, 1H), 1.57 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (75 MHz) δ 214.2 (C), 172.2 (C), 135.1 (CH), 129.8 (CH), 109.2 (C), 82.9 (CH), 78.8 (CH), 58.2 (C), 52.5 (CH_3), 50.7 (CH), 41.2 (C), 39.5 (CH), 36.9 (CH), 33.6 (CH_2), 25.5 (CH_3), 25.0 (CH_3), 22.3 (CH_3), 18.6 (CH_3).

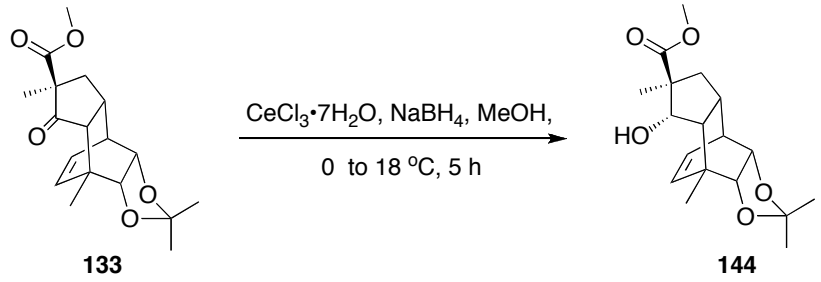
IR ν_{max} 2936, 2876, 1748, 1728, 1458, 1375, 1268, 1209, 1165, 1065, 999, 883, 728 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 320 ($M^{+\bullet}$, 8%), 305 (55), 262 (87), 220 (60), 202 (55), 173 (61), 157 (73), 134 (96), 105 (100).

HREIMS Found: $M^{+\bullet}$, 320.1637. $C_{18}H_{24}O_5$ requires $M^{+\bullet}$, 320.1624.

Optical Rotation $[\alpha]_D$ = +11 (*c* 0.2, $CHCl_3$).

Methyl (3a*R*,4*R*,4a*R*,5*S*,6*S*,7a*R*,8*S*,8a*S*)-5-hydroxy-2,2,4,6-tetramethyloctahydro-3a*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxole-6-carboxylate (144)



133 **144**

A solution of $CeCl_3 \cdot 7H_2O$ (16.01 g, 43.0 mmol) and ketone **133** (6.88 g, 21.5 mmol) in MeOH (107 mL) was cooled to 0 °C then treated in portions, over 30 min, with $NaBH_4$ (1.63 g, 43.0 mmol). The resulting mixture was allowed to warm to 18 °C, stirred at this temperature for 2 h then re-cooled to 0 °C and treated with an additional aliquot of $NaBH_4$ (1.68 g, 44.5 mmol). The reaction mixture was then re-warmed to 18 °C, stirred at this temperature for an additional 2 h then diluted (SLOWLY) with water (20 mL). After hydrogen evolution had ceased the reaction mixture was concentrated under reduced pressure and the residue extracted with CH_2Cl_2 (4 × 150 mL). The combined organic extracts were washed with water (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the *title hydroxy-ester* ***144*** (6.30 g, 91%) as a low-melting solid, (R_f = 0.2, 3:7 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 6.10 (m, 2H), 4.28 (dd, *J* = 11.5 and 5.9 Hz, 1H), 4.20 (dd, *J* = 7.0 and 3.3 Hz, 1H), 3.82 (d, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 2.81 (m, 1H), 2.24–2.08 (complex m, 2H), 1.93 (dd, *J* = 10.5 and 5.9 Hz, 1H), 1.56 (d, *J* = 6.6 Hz, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H), 1.08 (br t, *J* = 11.5 Hz, 1H).

^{13}C NMR (75 MHz) δ 176.9 (C), 137.7 (CH), 130.7 (CH), 109.0 (C), 83.3 (CH), 79.9 (CH), 77.6 (CH), 56.6 (CH_3), 52.0 (C), 50.7 (CH), 40.6 (two signals overlapping, CH and C), 37.9 (CH), 37.4 (CH_2), 25.4 (CH_3), 24.8 (CH_3), 19.6 (CH_3), 18.3 (CH_3).

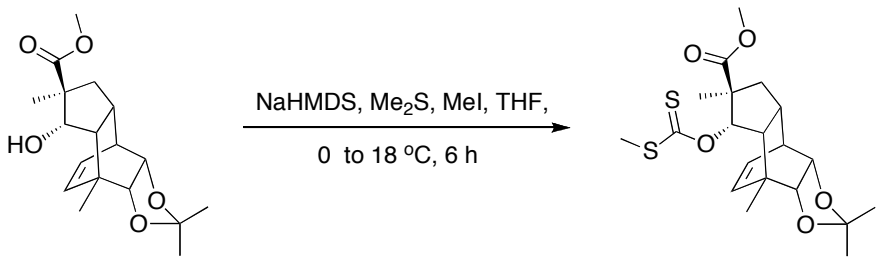
IR ν_{max} 3541, 2974, 2934, 2877, 1728, 1457, 1377, 1277, 1256, 1207, 1163, 1080, 1054, 1038, 980, 895, 877, 825, 728 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 322 ($M^{+\bullet}$, 2%), 307 (62), 264 (99), 222 (100), 187 (87), 186 (99), 144 (87), 117 (60), 106 (81), 91 (68), 85 (60), 43 (89).

HREIMS Found: $M^{+\bullet}$, 322.1780. $C_{18}H_{26}O_5$ requires $M^{+\bullet}$, 322.1780.

Optical Rotation $[\alpha]_D$ = -20 (*c* 1.0, $CHCl_3$).

Methyl (3a*R*,4*R*,4a*R*,5*S*,6*S*,7a*R*,8*S*,8a*S*)-2,2,4,6-tetramethyl-5-{[(methylthio)carbonothioyl]oxy}octahydro-3a*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxole-6-carboxylate (144a)



144 **144a**

A solution of alcohol **144** (1.91 g, 5.91 mmol) in THF (60 mL) was cooled to 0 °C then treated with NaHMDS (11.8 mL of a 1.0 M solution in THF, 11.8 mmol). The ensuing mixture was stirred at 0 °C for 1.5 h, warmed to 18 °C over 30 min then re-cooled to 0 °C and treated with carbon disulfide (711 mL, 11.8 mmol). After stirring at 0 °C for 1.5 h the reaction mixture was warmed to 18 °C over 30 min then immediately re-cooled to 0 °C and treated with iodomethane (773 mL, 12.4 mmol). Stirring was continued at 0 °C for 1.5 then the reaction mixture was warmed to 18 °C, stirred at this temperature for 30 min then diluted with Et_2O (60 mL) and washed with water (100 mL), HCl (100 mL of a 1.0 M aqueous solution) and brine (50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil. The bulk of this material was subjected, as obtained, to the next step of the reaction sequence as detailed in the following Section. For the purposes of characterization, a sample of this material was subjected to flash column chromatography (silica, 1:9 → 3:7 *v/v* EtOAc/hexane gradient elution). Concentration of the relevant fractions (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded the *title xanthate ester **144a*** as a light-yellow oil.

^{1}H NMR (300 MHz) δ 6.64 (d, *J* = 5.1 Hz, 1H), 5.91 (m, 2H), 4.20 (dd, *J* = 7.2 and 3.0 Hz, 1H), 3.79 (d, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 2.80 (m, 1H), 2.60 (s, 3H), 2.24–2.05 (complex m, 3H), 1.42 (t, *J* = 10.3 Hz, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (75 MHz) δ 216.1 (C), 175.6 (C), 137.2 (CH), 125.9 (CH), 109.1 (C), 86.2 (CH), 83.6 (CH), 79.6 (CH), 57.0 (C), 52.4 (CH_3), 50.0 (CH), 40.3 (CH), 40.0 (C), 39.4 (CH_2), 37.5 (CH), 25.5 (CH_3), 25.0 (CH_3), 19.6 (CH_3), 19.2 (CH_3), 18.3 (CH_3).

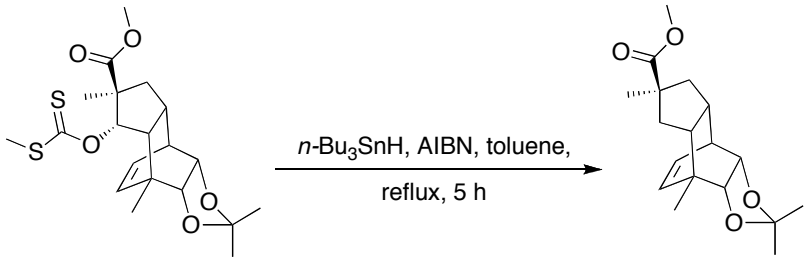
IR ν_{max} 2975, 2932, 1730, 1457, 1377, 1286, 1245, 1207, 1057, 877, 729 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 412 ($M^{+\bullet}$, 43%), 379 (44), 246 (51), 187 (85), 186 (75), 159 (48), 145 (82), 144 (83), 91 (100), 43 (46).

HREIMS Found: $M^{+\bullet}$, 412.1387. $C_{20}H_{28}O_5S$ requires $M^{+\bullet}$, 412.1378.

Optical Rotation $[\alpha]_D$ = +64 (*c* 0.5, $CHCl_3$).

Methyl (3a*R*,4*R*,4a*R*,6*S*,7a*S*,8*S*,8a*S*)-2,2,4,6-tetramethyloctahydro-3a*H*-4,8-ethenoindeno-[5,6-*d*][1,3]dioxole-6-carboxylate (145)



144a **145**

A solution of xanthate ester **144a** (*ca.* 5.91 mmol, obtained as described immediately above) in toluene (100 mL) was treated with AIBN (20 mg, 0.122 mmol) and tri-*n*-butyltin hydride (3.2 mL, 11.9 mmol) and the ensuing mixture heated under reflux for 1.5 h then cooled to 18 °C and treated with additional aliquots of AIBN (20 mg, 0.122 mmol) and tri-*n*-butyltin hydride (3.2 mL, 11.9 mmol). The resulting mixture was again heated under reflux, this time for 3.5 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, hexane then 1:4 *v/v* EtOAc/hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.4, 3:7 *v/v* EtOAc/hexane), the *title compound **145*** (1.76 g, 97% from alcohol **144**) as a white crystalline solid, m.p. = 63–64 °C

^{1}H NMR (300 MHz) δ 6.00 (br t, *J* = 8.0 Hz, 1H), 5.74 (dd, *J* = 8.0 and 1.0 Hz, 1H), 4.18 (ddd, *J* = 8.1, 3.6 and 3.2 Hz, 1H), 3.79 (dd, *J* = 8.1 and 0.9 Hz, 1H), 3.64 (s, 3H), 2.72 (m, 1H), 2.23–2.07 (complex m, 3H), 1.79 (m, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.01 (m, 2H).

^{13}C NMR (75 MHz) δ 178.5 (C), 135.6 (CH), 130.3 (CH), 108.8 (C), 83.4 (CH), 79.7 (CH), 51.9 (CH_3), 50.8 (C), 45.2 (CH), 41.8 (CH_2), 41.5 (C), 40.5 (CH), 40.4 (CH_2), 38.7 (CH), 25.6 (CH_3), 24.9 (CH_3), 23.8 (CH_3), 19.7 (CH_3).

IR ν_{max} 2960, 2932, 2873, 1731, 1456, 1377, 1254, 1206, 1168, 1101, 1065, 1031, 879 cm^{-1}.

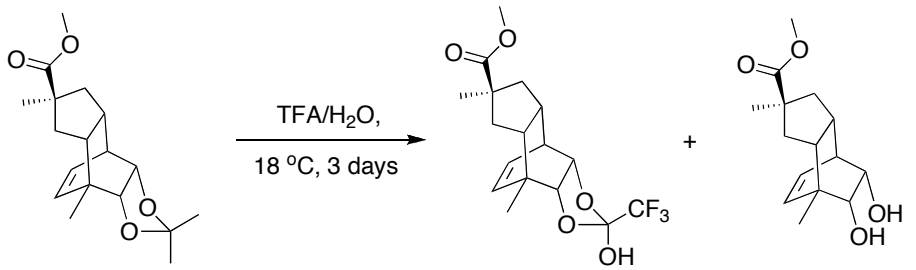
Mass spectrum (EI, 70 eV) *m/z* 291 [$(M - CH_3\cdot)^+$, 73%], 248 (77), 206 (95), 189 (83), 188 (92), 173 (73), 159 (100), 146 (92), 145 (91), 144 (92), 131 (90), 109 (64), 105 (70), 100 (77), 91 (82), 43 (67).

HREIMS Found: $(M - CH_3\cdot)^+$, 291.1589. $C_{18}H_{26}O_4$ requires $(M - CH_3\cdot)^+$, 291.1589.

Elemental Analysis Found: C, 70.16; H, 8.07. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55%.

Optical Rotation $[\alpha]_D$ = *ca.* 0 (*c* 1.2, $CHCl_3$).

Methyl (2*S*,3a*R*,4*R*,4a*R*,6*S*,7a*S*,8*S*,8a*S*)-2-hydroxy-4,6-dimethyl-2-(trifluoromethyl)-octahydro-3a*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxole-6-carboxylate (146) and methyl (2*S*,3a*R*,4*R*,7*S*,7a*S*,8*S*,9*R*)-8,9-dihydroxy-2,4-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethanoindene-2-carboxylate (148)



145 **146** **148**

A solution of acetonide **145** (122 mg, 0.39 mmol) in TFA (2 mL) and water (5 drops) was stirred at 18 ºC for 3 days then concentrated under reduced pressure and any residual TFA removed azeotropically using toluene. Subjection of the resulting solid to flash column chromatography (silica, 1:9 → 1:1 *v/v* EtOAc/hexane gradient elution), afforded three fractions, A, B and C.

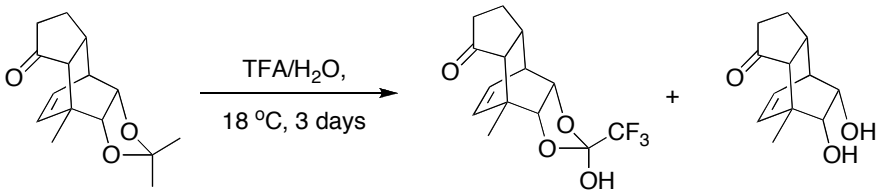
Concentration of fraction A (R_f = 0.5, 3:7 *v/v* EtOAc/hexane) gave the starting acetonide **145** (9.5 mg, 8% recovery) as a white crystalline solid. This material was identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.3 in 3:7 *v/v* EtOAc/hexane) afforded *hemiorthoester **146*** (98 mg, 74% at 92% conversion) as clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.21 (m, 1H), 5.95 (dm, *J* = 8.4 Hz, 1H), 4.43 (ddd, *J* = 7.5, 3.3 and 0.9 Hz, 1H), 4.04 (dd, *J* = 7.5 and 1.2 Hz, 1H), 3.65 (s, 3H), 2.89 (m, 1H), 2.29–2.08 (complex m, 3H), 1.83 (m, 1H), 1.25 (s, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.07–0.92 (m, 2H).
^{13}C NMR (75 MHz) δ 178.1 (C), 136.7 (CH), 131.6 (CH), 85.4 (CH), 81.7 (CH), 52.0 (CH_3), 50.7 (C), 44.6 (CH), 41.9 (C), 41.7 (CH_2), 40.3 (CH_2), 39.8 (CH), 38.8 (CH), 23.7 (CH_3), 19.3 (CH_3) (signals due to CF_3 and hemiorthoester carbons not observed).
IR ν_{max} 3401, 2962, 2932, 1728, 1712, 1463, 1378, 1332, 1298, 1181, 1104, 1075, 1018, 978, 827, 731, 648 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 362 ($M^{+\bullet}$, 3%), 303 (23), 206 (95), 174 (78), 159 (68), 146 (100), 131 (85), 105 (63), 101 (69), 91 (69).
HREIMS Found: $M^{+\bullet}$, 362.1332. $C_{17}H_{21}F_3O_5$ requires $M^{+\bullet}$, 362.1341.

Concentration of fraction C (R_f = 0.1, 3:7 *v/v* EtOAc/hexane) gave *diol* ***148*** (8 mg, 7% at 92% conversion) as a white, crystalline solid. This material was identical, in all respects, with authentic material that was prepared at a later stage.

(2*S*,3a*R*,4*R*,4a*R*,7a*R*,8*S*,8a*S*)-2-Hydroxy-4-methyl-2-(trifluoromethyl)octahydro-5*H*-4,8-ethenoindeno[5,6-*d*][1,3]dioxol-5-one (147) and (3a*R*,4*S*,7*R*,7a*R*,8*R*,9*S*)-8,9-dihydroxy-7-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethanoinden-1-one (147a)



81 **147** **147a**

A solution of acetonide **81** (102 mg, 0.41 mmol) in TFA (2 mL) and water (5 drops) was stirred at 18 ºC for 3 days then concentrated under reduced pressure and any residual TFA removed azeotropically using toluene. Subjection of the resulting solid to flash column chromatography (silica, 2:8 → 1:1 *v/v* EtOAc/hexane gradient elution), afforded three fractions, A, B and C.

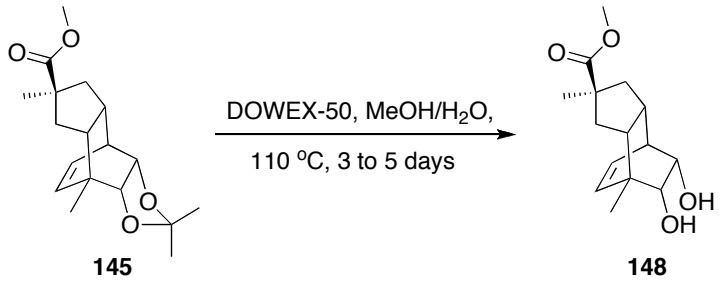
Concentration of fraction A (R_f = 0.25, 3:7 *v/v* EtOAc/hexane) gave the starting acetonide **81** (4.5 mg, 4% recovery) as a white crystalline solid. This material was identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.1, 3:7 *v/v* EtOAc/hexane) afforded a white solid that upon recrystallization (MeOH) gave *hemiorthoester* ***147*** (104 mg, 87% at 96% conversion) as a white, crystalline solid, m.p. = 180–181 °C.

^{1}H NMR (300 MHz) δ 6.32 (m, 1H), 5.98 (dm, *J* = 8.4 Hz, 1H), 4.51 (ddd, *J* = 7.5, 3.3 and 0.9 Hz, 1H), 4.07 (dd, *J* = 7.5 and 1.2 Hz, 1H), 3.26 (s, 1H), 3.09 (m, 1H), 2.49 (m, 1H), 2.20–2.00 (complex m, 3H), 1.95 (d, *J* = 9.6 Hz, 1H), 1.70 (m, 1H), 1.52 (s, 3H).
^{13}C NMR (75 MHz) δ 218.2 (C), 136.5 (CH), 131.1 (CH), 84.6 (CH), 80.8 (CH), 51.3 (CH), 42.1 (C), 40.6 (CH), 39.2 (CH_2), 35.7 (CH), 24.9 (CH_2), 18.4 (CH_3) (signals due to CF_3 and hemiorthoester carbons not observed).
IR ν_{max} 3118, 2938, 1714, 1262, 1238, 1174, 1077, 1056, 987, 819, 741, 729, 651 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 304 ($M^{+\bullet}$, 4%), 149 (38), 148 (100), 120 (55), 106 (90), 105 (73), 92 (85), 91 (65), 56 (70).
HREIMS Found: $M^{+\bullet}$, 304.0932. $C_{14}H_{15}F_3O_4$ requires $M^{+\bullet}$, 304.0922.

Concentration of fraction C (R_f << 0.1 in 3:7 *v/v* EtOAc/hexane) gave *diol* ***147a*** (3 mg, 6% at 96% conversion) as a white, crystalline solid. The spectral data acquired on this compound matched those reported by Stewart.[26]

Methyl (2*S*,3a*R*,4*R*,7*S*,7a*S*,8*S*,9*R*)-8,9-dihydroxy-2,4-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethanoindene-2-carboxylate (148)



145 **148**

A solution of acetonide **145** (507 mg, 1.65 mmol) in MeOH/water (12 mL of a 5:1 *v/v* mixture) was treated with DOWEX-50 resin [500 mg that had been washed, successively, with $NaHCO_3$ (saturated aqueous solution), water (distilled), HCl (1.0 M aqueous solution) and water (distilled)]. The ensuing mixture was heated at 110 °C until tlc analysis revealed that the staring material had been consumed (normally 3–5 days). The cooled reaction mixture was filtered and the resin thus retained washed with MeOH (3 × 10 mL). The combined filtrates were concentrated under reduced pressure then the residue diluted with NaCl (20 mL of a *ca.* 1.5 M aqueous solution) and the resulting mixture extracted with CH_2Cl_2 (5 × 20 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the *title diol* ***148*** (357 mg, 81%) as a clear, colourless oil (R_f = 0.2, 1:1 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 6.14 (dd, *J* = 8.3 and 6.5 Hz, 1H), 5.85 (dd, *J* = 8.3 and 1.1 Hz, 1H), 3.82 (dd, *J* = 7.4 and 2.3 Hz, 1H), 3.63 (s, 3H), 3.39 (d, *J* = 7.4 Hz, 1H), 2.86 (br s, 1H), 2.73 (br s, 1H), 2.68 (m, 1H), 2.22–2.13 (complex m, 3H), 1.82 (m, 1H), 1.16(8) (s, 3H), 1.16(6) (s, 3H), 0.93 (m, 2H).

^{13}C NMR (75 MHz) δ 178.5 (C), 136.5 (CH), 131.6 (CH), 74.7 (CH), 71.3 (CH), 51.9 (CH_3), 50.1 (C), 45.9 (CH), 42.8 (C), 41.9 (CH_2), 41.5 (CH), 40.9 (two signals overlapping, CH and CH_2), 23.7 (CH_3), 19.4 (CH_3).

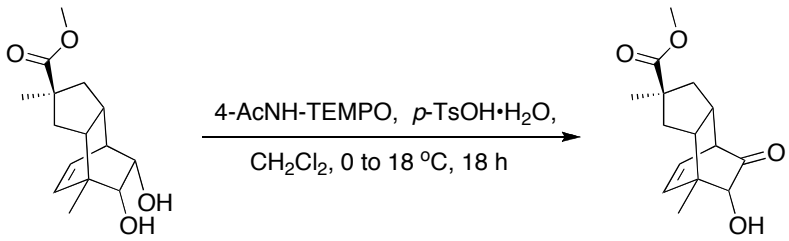
IR ν_{max} 3400, 2933, 1729, 1457, 1404, 1375, 1170, 1099, 1058, 1021, 995, 833, 791, 728 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 267 [$(M + H)^+$, 1%], 206 (94), 174 (56), 146 (100), 131 (90), 101 (45), 91 (35).

HREIMS Found: $(M + H)^+$, 267.1595. $C_{15}H_{22}O_4$ requires $(M + H)^+$, 267.1596.

Optical Rotation $[\alpha]_D$ = -5.5 (*c* 1.2, $CHCl_3$).

Methyl (2*S*,3a*R*,4*R*,7*S*,7a*S*,9*R*)-9-hydroxy-2,4-dimethyl-8-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethanoindene-2-carboxylate (149)



148 **149**

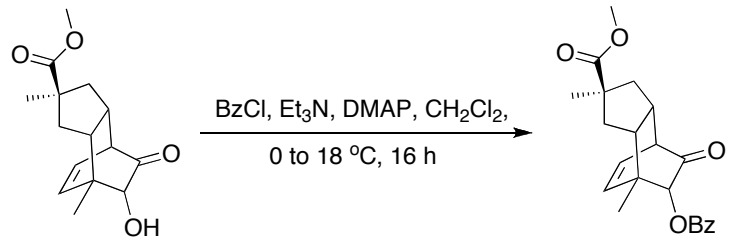
A solution of diol **148** (1.13 g, 4.25 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C then treated with *p*-TsOH•H_2O (1.76 g, 9.25 mmol). 4-Acetamido-TEMPO (1.97 g, 9.25 mmol) was then added, in portions over 2.5 h, to the reaction mixture which was then stirred at 0 °C for 2 h. After this time it was warmed to 18 °C, stirred at this temperature for 16 h then treated with $NaHCO_3$ (50 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an orange-coloured semi-solid. Subjection of this material to flash column chromatography (silica 1:9 →1:4 *v/v* EtOAc/hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A afforded the starting diol **148** (93 mg, 8% recovery) as a white crystalline solid (R_f = 0.2, 1:1 *v/v* EtOAc/hexane). This material was identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.4, 1:1 *v/v* EtOAc/hexane) afforded the *title acyloin* ***149*** (882 mg, 85% at 92% conversion) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.04 (m, 2H), 3.30 (s, 3H), 3.62 (s, 1H), 3.08 (dm, *J* = 9.9 Hz, 1H), 2.98 (br s, 1H), 2.55 (m, 1H), 2.32–2.14 (complex m, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.05 (m, 2H).
^{13}C NMR (75 MHz) δ 211.4 (C), 177.9 (C), 140.1 (CH), 126.2 (CH), 74.4 (CH), 52.0 (CH_3), 50.8 (CH), 50.1 (C), 47.3 (CH), 44.7 (C), 41.4 (CH_2), 40.7 (CH_2), 38.7 (CH), 23.6 (CH_3), 18.1 (CH_3).
IR ν_{max} 3462, 2962, 2931, 2872, 1729, 1463, 1450, 1374, 1325, 1286, 1199, 1171, 1080, 1037, 881, 818, 763, 721, 661 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 264 ($M^{+\bullet}$,7%), 233 (10), 199 (40), 140 (100), 43 (50).
HREIMS Found: $M^{+\bullet}$, 264.1361. $C_{15}H_{20}O_4$ requires $M^{+\bullet}$, 264.1362.
Optical Rotation $[\alpha]_D$ = +148 (*c* 0.1, $CHCl_3$).

Methyl (2*S*,3a*R*,4*R*,7*S*,7a*S*,9*R*)-9-(benzoyloxy)-2,4-dimethyl-8-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethanoindene-2-carboxylate (150)



149 **150**

A solution of the acyloin **149** (880 mg, 3.33 mmol) and 4-(*N,N*-dimethylamino)pyridine (1.43 g, 11.7 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C then treated with triethylamine (2.2 mL, 15.7 mmol) and benzoyl chloride (1.35 mL, 11.7 mmol). The ensuing mixture was warmed to 18 °C then stirred at this temperature for 16 h before being quenched with water (20 mL) then diluted with CH_2Cl_2 (50 mL). The separated organic phase was washed with $NaHCO_3$ (2 × 20 mL of a saturated aqueous solution) and brine (20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution) and so affording, after concentration of the appropriate fractions (R_f = 0.4, 3:7 *v/v* EtOAc/hexane), a white solid, recrystallization (*iso*-propanol) of which gave the *title benzoate* ***150*** (984 mg, 80%) as white needles, m.p. = 121–123 °C.

^{1}H NMR (300 MHz) δ 8.00 (dm, *J* = 7.8 Hz, 2H), 7.55 (m, 1H), 7.41 (tm, *J* = 7.8 Hz, 2H), 6.23 (br t, *J* = 7.5 Hz, 1H), 6.14 (dd, *J* = 7.5 and 0.6 Hz, 1H), 5.10 (s, 1H), 3.69 (s, 3H), 3.20 (ddd, *J*

= 6.5, 2.5 and 1.1 Hz, 1H), 2.73 (m, 1H), 2.49–2.29 (complex m, 3H), 1.30 (s, 3H), 1.16 (s, 3H), 1.13 (partially obscured m, 2H).

^{13}C NMR (75 MHz) δ 205.3 (C), 177.7 (C), 166.1 (C), 139.4 (CH), 133.2 (CH), 129.9 (CH), 129.4 (C), 128.3 (CH), 127.0 (CH), 74.0 (CH), 52.1 (CH_3), 51.6 (CH), 50.2 (C), 47.0 (CH), 43.8 (C), 41.6 (CH_2), 40.9 (CH_2), 39.2 (CH), 23.7 (CH_3), 18.3 (CH_3).

IR ν_{max} 2965, 2932, 1740, 1725, 1450, 1325, 1268, 1197, 1172, 1110, 1070, 1028, 985 cm^{-1}.

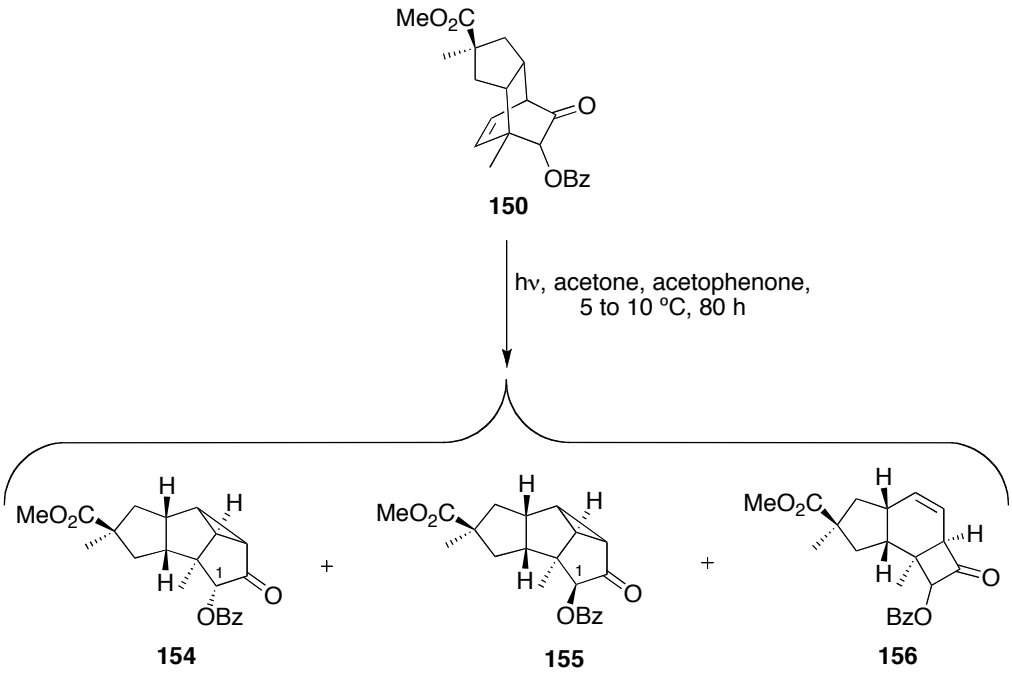
Mass spectrum (EI, 70 eV) *m/z* 368 ($M^{+\bullet}$, 1%), 309 (12), 246 (51), 218 (51), 206 (25), 186 (18), 174 (26), 159 (37), 158 (75), 146 (55), 131 (20), 106 (45), 105 (100), 91 (20), 77 (70).

HREIMS Found: $M^{+\bullet}$, 368.1625. $C_{22}H_{24}O_5$ requires $M^{+\bullet}$, 368.1624.

Elemental Analysis Found: C, 71.24; H, 6.54. $C_{22}H_{24}O_5$ requires C, 71.72; H, 6.57%.

Optical Rotation $[\alpha]_D$ = +179 (*c* 1.0, $CHCl_3$).

Methyl (1*R*,2a*R*,2b*R*,2c*R*,4*S*,5a*R*,5b*S*,5c*S*)-1-(benzoyloxy)-4,5b-dimethyl-2-oxodecahydro-1*H*-cyclopenta[*a*]cyclopropa[*cd*]pentalene-4-carboxylate (154), methyl (1*S*,2a*R*,2b*R*,2c*R*,4*S*,5a*R*,5b*S*,5c*S*)-1-(benzoyloxy)-4,5b-dimethyl-2-oxodecahydro-1*H*-cyclopenta[*a*]cyclopropa[*cd*]pentalene-4-carboxylate (155) and methyl (1*S*/*R*,2a*R*,4a*R*,6*S*,7a*R*,7b*S*)-1-(benzoyloxy)-6,7b-dimethyl-2-oxo-2,2a,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]indene-6-carboxylate (156)



A deoxygenated solution of compound **150** (217 mg, 0.59 mmol) and acetophenone (172 mL, 1.47 mmol) in acetone (120 mL) contained in a Pyrex™ vessel jacketed by a water-cooled (5–10 °C) solution of sodium bromide (750 g) and lead(II) nitrate (8 g) in water (1000 mL) was subjected to irradiation with a Philips 125 W HPL-N lamp for 80 h. The reaction mixture was then concentrated under reduced pressure and the ensuing pale-yellow oil subjected to flash column chromatography (silica, 5:95 → 3:7 *v/v* EtOAc/hexane gradient elution) and thus affording three fractions, A, B and C.

Concentration of fraction A [R_f = 0.3(5), 3:7 *v/v* EtOAc/hexane] afforded the *title 1*(R)-*tetracycle **154*** (19.2 mg, 9%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 8.05 (m, 2H), 7.57 (tt, *J* = 7.5 and 1.5 Hz, 1H), 7.43 (tm, *J* = 7.5 Hz, 2H), 4.92 (br s, 1H), 3.68 (s, 3H), 2.82 (ddd, *J* = 13.8, 9.3 and 2.1 Hz, 1H), 2.65 (m, 1H), 2.53 (t, *J* = 6.0 Hz, 1H), 2.39 (m, 1H), 2.23 (m, 2H), 1.79 (dd, *J* = 10.2 and 6.0 Hz, 1H), 1.57 (m, 1H), 1.36 (s, 3H), 1.30 (m, 1H), 1.19 (s, 3H).

^{13}C NMR (75 MHz) δ 209.7 (C), 177.7 (C), 165.6 (C), 133.3 (CH), 129.9 (CH), 129.4 (C), 128.4 (CH), 84.3 (CH), 60.1 (CH), 52.2 (CH_3), 51.6 (C), 50.9 (C), 44.6 (CH_2), 43.4 (CH), 40.8 (CH), 40.6 (CH_2), 39.5 (CH), 39.0 (CH), 25.0 (CH_3), 15.4 (CH_3).

IR ν_{max} 2919, 1726, 1451, 1315, 1266, 1197, 1175, 1106, 1069, 1026, 711 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 368 ($M^{+\bullet}$, 5%), 309 (12), 263 (38), 246 (68), 218 (47), 206 (52), 203 (56), 159 (63), 158 (93), 146 (75), 145 (55), 106 (81), 105 (95), 77 (100).

HREIMS Found: $M^{+\bullet}$, 368.1623. $C_{22}H_{24}O_5$ requires $M^{+\bullet}$, 368.1624.

Optical Rotation $[\alpha]_D$ = +35 (*c* 0.6, $CHCl_3$).

Concentration of fraction B [R_f = 0.3(0), 3:7 *v/v* EtOAc/hexane] afforded the *title 1*(S)-*tetracycle* ***155*** (178 mg, 82%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 8.02 (dm, *J* = 7.8 Hz, 2H), 7.57 (tt, *J* = 7.8 and 1.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.34 (d, *J* = 1.5 Hz, 1H), 3.65 (s, 3H), 2.77 (ddd, *J* =13.8, 9.3 and 2.4 Hz, 1H), 2.67–2.49 (complex m, 2H), 2.29 (t, *J* = 5.4 Hz, 1H), 2.14–2.04 (complex m, 2H), 1.79 (dd, *J* = 10.2 and 5.4 Hz, 1H), 1.55 (t, *J* = 12.0 Hz, 1H), 1.36 (s, 3H), 1.33 (m, 1H), 1.25 (s, 3H).

^{13}C NMR (75 MHz) δ 206.1 (C), 177.8 (C), 165.4 (C), 133.4 (CH), 129.9 (CH), 129.3 (C), 128.4 (CH), 83.1 (CH), 54.2 (CH), 52.0 (CH_3), 51.5 (C), 49.7 (C), 44.5 (CH_2), 43.0 (CH), 40.4 (CH_2), 36.0 (CH), 33.6 (CH), 32.5 (CH), 24.8 (CH_3), 20.6 (CH_3).

IR ν_{max} 2928, 1740, 1725, 1451, 1314, 1269, 1176, 1112, 1071, 999, 711 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 368 ($M^{+\bullet}$, 66%), 309 (16), 263 (61), 246 (25), 203 (35), 106 (50), 105 (100), 77 (78).

HREIMS Found: $M^{+\bullet}$, 368.1622. $C_{22}H_{24}O_5$ requires $M^{+\bullet}$, 368.1624.

Optical Rotation $[\alpha]_D$ = -75 (*c* 0.4, $CHCl_3$).

Concentration of fraction C (R_f = 0.5, 3:7 *v/v* EtOAc/hexane) afforded the *title cyclobutanone* ***156*** (traces) as a clear, colourless oil. This material is unstable and decomposes on standing at 18 °C in air for short periods of time.

^{1}H NMR (300 MHz) δ 8.07 (dm, *J* = 7.2 Hz, 2H), 7.60 (tt, *J* = 7.2 and 1.5 Hz, 1H), 7.45 (tm, *J* = 7.2 Hz, 2H), 5.94 (d, *J* = 3.0 Hz, 1H), 5.74 (dm, *J* = 10.0 Hz, 1H), 5.63 (ddd, *J* = 10.0, 4.8 and 2.7 Hz, 1H), 3.68 (s, 3H), 3.18 (m, 1H), 3.02 (m, 1H), 2.74–2.60 (complex m, 2H), 2.35 (dd, *J* = 13.0 and 7.2 Hz, 1H), 1.67 (dd, *J* = 13.0 and 1.5 Hz, 1H), 1.29 (s, 3H), 1.19 (s, 3H), 1.18 (partially obscured m, 1H).

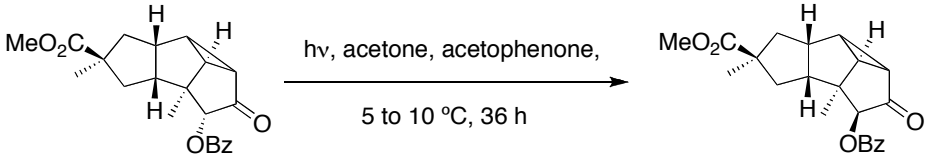
^{13}C NMR (75 MHz) δ 200.3 (C), 178.8 (C), 165.0 (C), 133.6 (CH), 133.3 (CH), 130.0 (CH), 128.7 (C), 128.5 (CH), 118.5 (CH), 82.9 (CH), 57.7 (CH), 52.1 (CH_3), 48.4 (C), 43.6 (CH_2), 42.2 (CH), 40.4 (CH_2), 38.2 (CH), 37.1 (C), 27.7 (CH_3), 19.2 (CH_3).

IR ν_{max} 2954, 2873, 1790, 1727, 1451, 1267, 1217, 1165, 1107, 1025, 990, 710 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 325 [(M – CO – CH_3•)$^+$, < 1%], 246 (28), 206 (37), 159 (50), 158 (99), 146 (72), 145 (59), 106 (53), 105 (67), 77 (100).

HREIMS Found: (M – CO – CH_3•)$^+$, 325.1436. $C_{22}H_{24}O_5$ requires (M – CO – CH_3•)$^+$, 325.1440.

Methyl (1*S*,2a*R*,2b*R*,2c*R*,4*S*,5a*R*,5b*S*,5c*S*)-1-(benzoyloxy)-4,5b-dimethyl-2-oxodecahydro-1*H*-cyclopenta[*a*]cyclopropa[*cd*]pentalene-4-carboxylate (154)

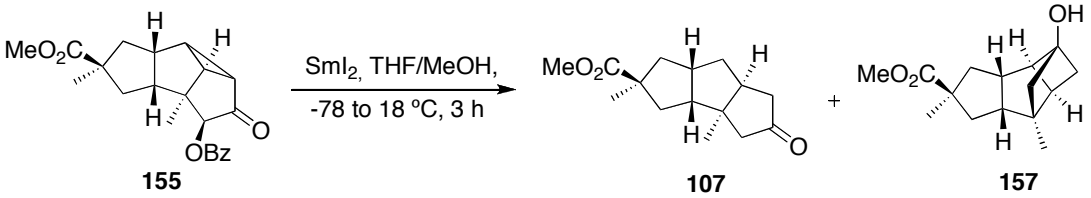


154 **155**

A sample of compound **154** (50.4 mg, 0.14 mmol) was subjected to the irradiation for 36 h under the conditions defined immediately above. Work-up followed by chromatographic purification afforded isomer **155** (48.9 mg, 97%). This material proved identical, in all respects, with authentic material.

Methyl (2*S*,3a*R*,3b*R*,6a*S*,7a*S*)-2,3b-dimethyl-5-oxodecahydro-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (107) and methyl (2*S*,2a*R*,2b*S*,4*S*,5a*R*,6*S*,6a*R*)-2-hydroxy-4,6-dimethyldecahydro-2,6-methanocyclobuta[*a*]pentalene-4-carboxylate (157)

Method 1:



155 **107** **157**

A solution of cyclopropane **155** (67 mg, 0.18 mmol) in THF/MeOH (1.5 mL of a 2:1 *v/v* mixture) was cooled to −78 °C then treated with samarium(II) iodide (7.28 mL of a 0.1 M solution in THF, 0.73 mmol). The ensuing mixture was stirred at −78 °C for 1 h then warmed to 18 °C and stirred at the latter temperature for a further 2 h and after which time the initial blue colour of the reaction mixture had been discharged. The reaction mixture so obtained was treated with K_2CO_3 (5 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic fractions were washed with water (5 mL) and brine (5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced

pressure. The ensuing pale-yellow oil was subjected to flash column chromatography (silica, 1:9 *v/v* Et_2O/hexane elution) to yield two fractions, A and B.

Concentration of fraction A (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded the title triquinane **107** (25.5 mg, 56%) as a clear, colourless oil.

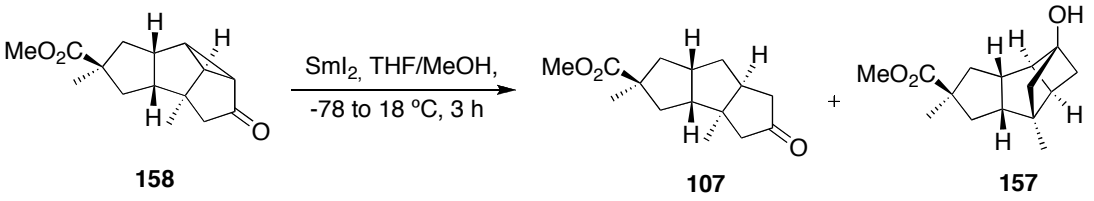
^{1}H NMR (300 MHz) δ 3.66 (s, 3H), 2.70 (m, 1H), 2.60–2.34 (complex m, 4H), 2.24–2.06 (complex m, 3H), 2.03 (d, *J* = 7.2 Hz, 2H), 1.70 (m, 1H), 1.58–1.44 (complex m, 1H), 1.30 (s, 3H), 1.06 (m, 1H), 1.04 (s, 3H).
^{13}C NMR (75 MHz) δ 220.2 (C), 178.0 (C), 52.9 (CH), 52.0 (C), 51.9 (CH_3), 51.2 (CH_2), 49.1 (C), 46.0 (CH_2), 44.5 (CH), 42.9 (CH_2), 41.4 (CH), 40.6 (CH_2), 39.6 (CH_2), 24.4 (CH_3), 22.1 (CH_3).
IR ν_{max} 2950, 1740, 1460, 1406, 1377, 1306, 1251, 1196, 1168, 1080, 846 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 3%), 248 (2), 192 (100), 133 (75), 105 (61).
HREIMS Found: $M^{+\bullet}$, 250.1570. $C_{15}H_{22}O_3$ requires $M^{+\bullet}$, 250.1569.
Optical Rotation $[\alpha]_D$ = −121 (*c* 0.2, $CHCl_3$) [lit.[71] $[\alpha]_D$ = −125 (*c* 1.2, $CHCl_3$)].

The data presented above matched the equivalent spectral information reported in the literature.[71]

Concentration of fraction B (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded the *title cyclobutanol **157*** (11.4 mg, 25%) as a white crystalline solid, m.p. = 79–82 °C.

^{1}H NMR (300 MHz) δ 3.62 (s, 3H), 2.52–2.24 (complex m, 3H), 2.14 (br s, 1H), 2.04 (ddd, *J* = 12.6, 7.2 and 2.7 Hz, 1H), 1.91 (t, *J* = 3.0 Hz, 1H), 1.89 (dd, *J* = 3.6 and 1.5 Hz, 1H), 1.64 (s, 1H), 1.57 (m, 1H), 1.38 (dd, *J* = 9.6 and 1.5 Hz, 1H), 1.24 (s, 3H), 1.06 (m, 1H), 1.01 (s, 3H), 0.93 (m, 1H), 0.87 (m, 1H).
^{13}C NMR (75 MHz) δ 178.4 (C), 77.9 (C), 63.3 (CH), 58.5 (CH), 51.9 (CH_3), 51.8 (C), 48.0 (C), 44.9 (CH_2), 42.9 (CH_2), 39.5 (CH), 39.4 (CH_2), 39.2 (CH_2), 36.9 (CH), 24.3 (CH_3), 18.2 (CH_3).
IR ν_{max} 3424, 2951, 2870, 1730, 1463, 1450, 1375, 1331, 1312, 1287, 1247, 1222, 1195, 1168, 1106, 1091, 875, 774, 763, 701 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 2%), 235 (3), 207 (13), 193 (76), 147 (50), 133 (100).
HREIMS Found: $M^{+\bullet}$, 250.1576. $C_{15}H_{22}O_3$ requires $M^{+\bullet}$, 250.1569.
Optical Rotation $[\alpha]_D$ = +6 (*c* 0.9, $CHCl_3$).

Method 2:



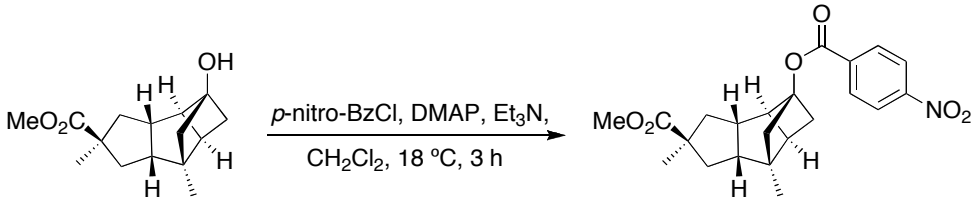
158 **107** **157**

A solution of cyclopropane **158** (293 mg, 1.18 mmol, obtained as described on page 162) in THF/MeOH (15 mL of a 2:1 *v/v* mixture) was cooled to −78 °C then treated with samarium(II) iodide (24 mL of a 0.1 M solution in THF, 2.4 mmol). The ensuing mixture was treated in the same manner as detailed immediately above in Method 1 and thus affording a pale-yellow oil upon work-up. Subjection of this material to flash column chromatography (silica, 1:9 *v/v* Et_2O/hexane elution) yielded two fractions, A and B.

Concentration of fraction A (R_f = 0.4, 3:7 *v/v* EtOAc/hexane) afforded triquinane **107** (173 mg, 59%) as a clear, colourless oil. This material was identical, in all respects, with that obtained *via* Method 1.

Concentration of fraction B (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded cyclobutanol **157** (74 mg, 25%) as a white crystalline solid. This material was identical, in all respects, with that obtained *via* Method 1.

Methyl (2*S*,2a*R*,2b*S*,4*S*,5a*R*,6*S*,6a*R*)-4,6-dimethyl-2-[(4-nitrobenzoyl)oxy]decahydro-2,6-methanocyclobuta[*a*]pentalene-4-carboxylate (157a)



157 **157a**

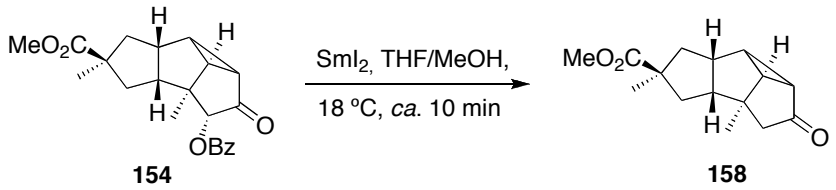
A solution of alcohol **157** (20 mg, 0.08 mmol) and 4-(*N,N*-dimethylamino)pyridine (34 g, 0.28 mmol) in CH_2Cl_2 (2 mL) was treated with triethylamine (30 mL, 0.22 mmol) and freshly prepared *p*-nitrobenzoyl chloride (52 mg, 0.28 mmol). The ensuing mixture was stirred at 18 °C for 3 h before being quenched with water (2 mL) then diluted with CH_2Cl_2 (10 mL). The separated organic phase was washed with $NaHCO_3$ (2 mL of a saturated aqueous solution) and brine (2 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The

ensuing solid was recrystallized (hexane) to give the *title ester* ***157a*** (24 mg, 75%) as a white crystalline solid (R_f = 0.5, 3:7 *v/v* EtOAc/hexane), m.p. = 89–95 °C (with decomposition).

^{1}H NMR (300 MHz) δ 8.27 (d, *J* = 9.0 Hz, 2H), 8.16 (d, *J* = 9.0 Hz, 2H), 3.67 (s, 3H), 2.67 (q, *J* = 6.1 Hz, 1H), 2.56–2.34 (complex m, 3H), 2.20–1.98 (complex m, 3H), 1.78 (dd, *J* = 9.3 and 1.5 Hz, 1H), 1.56 (br s, 1H), 1.41 (br dd, *J* = 9.3 and 1.8 Hz, 1H), 1.27 (s, 3H), 1.10 (s, 3H), 1.00 (dd, *J* = 12.3 and 11.1 Hz, 1H), 0.90 (dd, *J* = 12.3 and 8.4 Hz, 1H).
^{13}C NMR (75 MHz) δ 178.2 (C), 163.7 (C), 150.4 (C), 136.0 (C), 130.7 (CH), 123.5 (CH), 81.6 (C), 61.3 (CH), 58.2 (CH), 51.9 (CH_3), 51.7 (C), 47.5 (C), 42.8 (CH_2), 42.0 (CH_2), 40.1 (CH), 39.1 (CH_2), 37.8 (CH), 37.7 (CH_2), 24.2 (CH_3), 18.1 (CH_3).
IR ν_{max} 2954, 2920, 2862, 1727, 1528, 1349, 1284, 1270, 1224, 1169, 1147, 1118, 872, 831, 718 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 399 ($M^{+\bullet}$, 2%), 340 (10), 339 (5), 249 (15), 232 (22), 193 (67), 150 (100), 120 (85).
HREIMS Found: $M^{+\bullet}$, 399.1684. $C_{22}H_{25}NO_6$ requires $M^{+\bullet}$, 399.1682.
Optical Rotation $[\alpha]_D$ = −19 (*c* 0.5, $CHCl_3$).

Methyl (2a*R*,2b*R*,2c*R*,4*S*,5a*R*,5b*S*,5c*S*)-4,5b-dimethyl-2-oxodecahydro-1*H*-cyclopenta[*a*]-cyclopropa[*cd*]pentalene-4-carboxylate (158)

Method 1:



154 **158**

A solution of compound **154** (185 mg, 0.50 mmol) in THF/MeOH (7.5 mL of a 2:1 *v/v* mixture) was cooled to −78 °C then treated, dropwise, with samarium(II) iodide (11 mL of 0.1 M solution in THF, 1.1 mmol) until a blue colour persisted (*ca*. 10 min). The reaction mixture was then poured into K_2CO_3 (10 mL of saturated aqueous solution) and the separated aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with water (10 mL) and brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the *title compound* ***158*** (122 mg, 98%) as a clear, colourless oil (R_f = 0.2, 3:7 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 3.64 (s, 3H), 2.76 (ddd, *J* = 13.8, 9.3 and 2.1 Hz, 1H), 2.56 (m, 1H), 2.37 (t, *J* = 5.4 Hz, 1H), 2.30 (dd, *J* = 18.0 and 1.2 Hz, 1H), 2.20–2.08 (complex m, 2H), 2.05–1.94 (complex m, 2H), 1.63 (dd, *J* = 10.2 and 6.3 Hz, 1H), 1.48 (t, *J* = 13.8 Hz, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.24 (br s, 1H).

^{13}C NMR (75 MHz) δ 214.5 (C), 178.1 (C), 63.0 (CH_2), 56.5 (CH), 52.0 (CH_3), 51.5 (C), 47.1 (C), 44.6 (CH_2), 43.1 (CH), 40.6 (CH_2), 40.0 (CH), 39.2 (CH), 38.6 (CH), 25.2 (CH_3), 22.1 (CH_3).

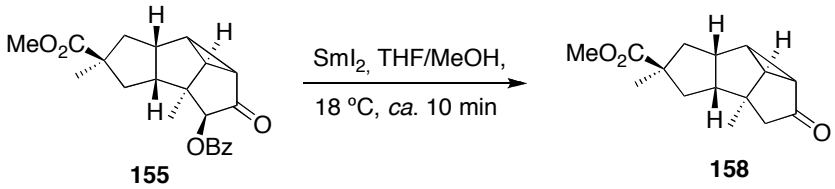
IR ν_{max} 2959, 2928, 2872, 1727, 1461, 1378, 1289, 1196, 1160, 1124, 1086, 958, 874, 808 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 248 ($M^{+\bullet}$, 16%), 206 (90), 174 (72), 146 (100), 131 (82).

HREIMS Found: $M^{+\bullet}$, 248.1414. $C_{15}H_{20}O_3$ requires $M^{+\bullet}$, 248.1412.

Optical Rotation $[\alpha]_D = -36$ (*c* 1.3, $CHCl_3$).

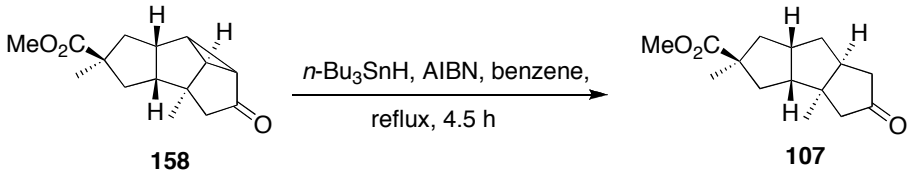
Method 2:



155 **158**

A sample of compound **155** (720 mg, 1.96 mmol) was subjected reaction with samarium(II) iodide at −78 °C under the conditions defined immediately above. Work-up provided the title compound **158** (470 mg, 97%) as a clear, colourless oil. This material was identical, in all respects, with the material generated by Method 1.

Methyl (2*S*,3a*R*,3b*R*,6a*S*,7a*S*)-2,3b-dimethyl-5-oxodecahydro-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (107)



158 **107**

A solution of cyclopropane **158** (756 mg, 3.04 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (95 mL) was treated, at 18 °C, with tri-*n*-butyltin hydride (1.64 mL, 6.09 mmol). The ensuing mixture was heated at reflux for 1.5 h then cooled to 18 °C and treated with further aliquots of AIBN (10 mg, 0.06 mmol) and tri-*n*-butyltin hydride (1.64 mL, 6.09 mmol) and refluxing of the reaction mixture continued for a further 1.5 h. This process was repeated once more and such that a total of six equivalents of tri-*n*-butyltin hydride were added to the original

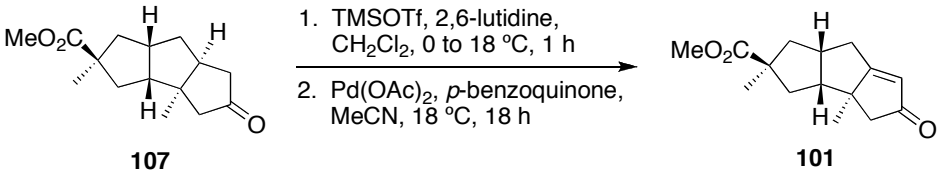
reaction mixture and a total reflux time of 4.5 h had been applied. The cooled reaction mixture was then concentrated under reduced pressure and the light-yellow oil so obtained subject to flash column chromatography (silica, 0:1 → 1:4 *v/v* EtOAc/hexane gradient elution) and thus providing two fractions, A and B.

Concentration of fraction A (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded compound **107** (580 mg, 88% at 87% conversion) as a clear, colourless oil. This material was identical, in all respects, with that obtained *via* the previous method.

Concentration of fraction B (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded the starting cyclopropane **158** (101 mg, 13% recovery) as a clear, colourless oil. This material was identical, in all respects, with authentic material.

Methyl (2*S*,3a*R*,3b*S*,7a*S*)-2,3b-dimethyl-5-oxo-2,3,3a,3b,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (101)

Method 1:



107 **101**

A solution of ketone **107** (51.5 mg, 0.21 mmol) and 2,6-lutidine (96 mL, 0.82 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C then treated, dropwise, with TMSOTf (112 mL, 0.62 mmol). The ensuing mixture was warmed to 18 °C, stirred for 1 h at this temperature then treated with water (2 mL) and CH_2Cl_2 (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic fractions then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a 4:1 mixture, as judged by ^{1}H NMR spectroscopic analysis, of silyl enol ethers as a light-yellow oil. A solution of these ethers in MeCN (1.5 mL) was added to a slurry of palladium (II) acetate (92 mg, 0.41 mmol) and *p*-benzoquinone (23 mg, 0.21 mmol) in MeCN (0.5 mmol). The ensuing mixture was stirred at 18 °C for 18 h then diluted with Et_2O (15 mL) and filtered through a pad of Celite™ contained in a sintered glass funnel. The solids thus retained were washed with additional Et_2O (3 × 5 mL) and the combined filtrates concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 *v/v* EtOAc/hexane elution) afforded two fractions, A and B.

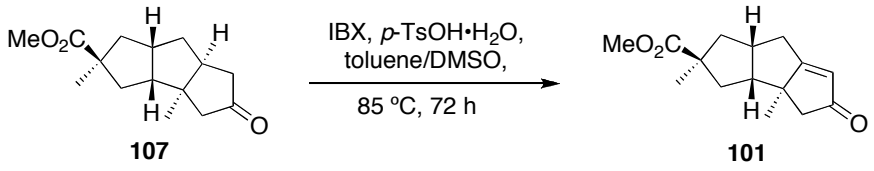
Concentration of the fraction A (R_f = 0.4, 3:7 *v/v* EtOAc/hexane) afforded the starting ketone **107** (16 mg, 31% recovery) as a clear, colourless oil. This material was identical, in all respects, with authentic material.

Concentration of the fraction B (R_f = 0.4, 1:1 *v/v* EtOAc/hexane) afforded the title enone **101** (35 mg, 85% at 69% conversion) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.68 (m, 1H), 3.66 (s, 3H), 2.84–2.63 (complex m, 2H), 2.52 (ddd, *J* = 12.3, 7.5 and 1.5 Hz, 1H), 2.44–2.21 (complex m, 3H), 2.27 (s, 2H), 1.53–1.39 (complex m, 1H), 1.35 (s, 3H), 1.24 (m, 1H), 1.10 (s, 3H).
^{13}C NMR (75 MHz) δ 210.5 (C), 195.0 (C), 178.0 (C), 122.5 (CH), 54.7 (C), 52.5 (CH_2), 52.0 (CH_3), 50.6 (CH), 49.2 (C), 46.3 (CH_2), 44.4 (CH), 37.1 (CH_2), 32.5 (CH_2), 24.5 (CH_3), 24.4 (CH_3).
IR ν_{max} 2960, 1728, 1709, 1635, 1467, 1202, 1169, 1093, 876 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 248 ($M^{+\bullet}$, 100%), 233 (32), 189 (75), 188 (70), 173 (63), 120 (70), 108 (92), 91 (55), 81 (68), 80 (82), 79 (68).
HREIMS Found: $M^{+\bullet}$, 248.1416. $C_{15}H_{20}O_3$ requires $M^{+\bullet}$, 248.1412.
Optical Rotation $[\alpha]_D$ = +56 (*c* 0.6, $CHCl_3$) [lit.[71] $[\alpha]_D$ = +57 (*c* 0.7, $CHCl_3$)].

The data presented above matched the equivalent spectral information reported in the literature.[71]

Method 2:



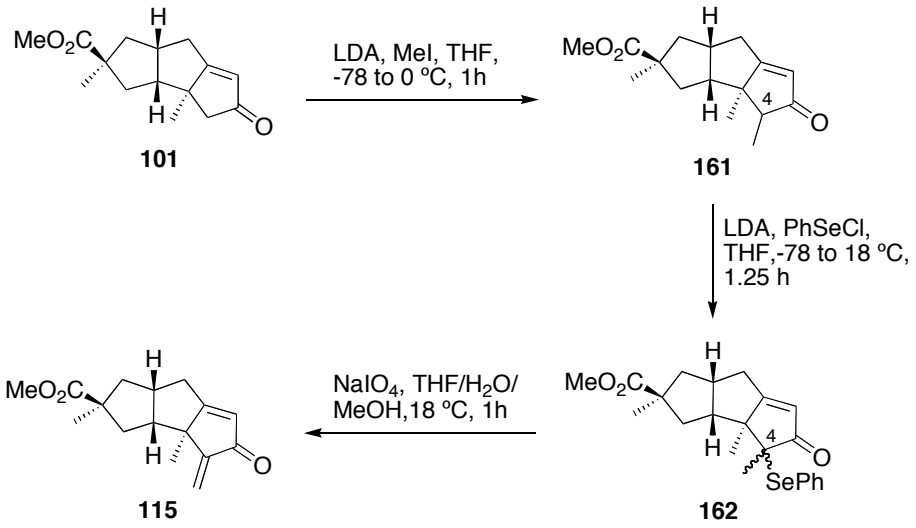
107 **101**

A solution of ketone **107** (462 mg, 1.88 mmol) in toluene/DMSO (7.5 mL of a 2:1 *v/v* mixture) was treated with *p*-TsOH•H_2O (105 mg, 0.55 mmol) and IBX (2.07 g, 7.38 mmol) and the resulting solution heated at 85 °C for 72 h then cooled and diluted with Et_2O (100 mL). The separated organic phase was washed with $NaHCO_3$ (2 × 5 mL of a 5% *w/v* aqueous solution), water (2 × 50 mL) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 *v/v* EtOAc/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.4, 1:1 *v/v* EtOAc/hexane), the title enone **101** (408 mg, 89%) as a

clear, colourless oil. This material was identical, in all respects, with that generated *via* Method 1.

Methyl (2*S*,3a*R*,3b*S*,7a*S*)-2,3b-dimethyl-4-methylene-5-oxo-2,3,3a,3b,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (115)

Method 1: [*via* **methyl (2*S*,3a*R*,3b*R*,7a*S*)-2,3b,4-trimethyl-5-oxo-2,3,3a,3b,4,5,7,7a-octahydro-1*H*-c yclopenta[*a*]pentalene-2-carboxylate (161) and methyl (2*S*,3a*R*,3b*S*,7a*S*)-2,3b,4-trimethyl-5-oxo-4-(phenylseleno)-2,3,3a,3b,4,5,7, 7a-octahydro-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (162)**]



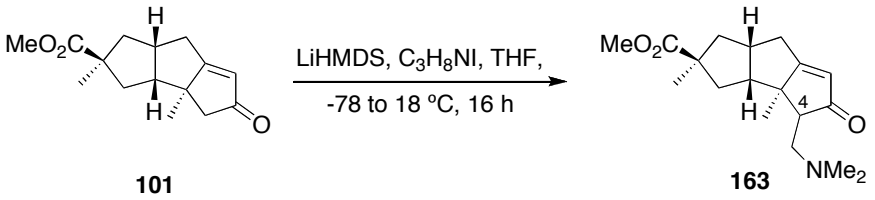
Step i: Following a procedure established by Ikegami *et al*.,[72] a solution of enone **101** (27 mg, 0.11 mmol) in THF (1 mL) was cooled to −78 °C then treated with freshly prepared LDA (513 mL of a 0.43 M solution in THF, 0.22 mmol). The ensuing mixture was stirred at −78 °C for 10 min then treated with iodomethane (68 mL, 1.09 mmol) after which it was allowed to warm to 0 °C over 1 h then quenched with NH_4Cl (2 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 5 mL). The combined organic fractions were washed with brine (5 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give methyl enone **161**[72] as a clear, colourless oil and as a single diastereoisomer of undetermined configuration at C4. This material was used directly in Step ii.

Step ii: A solution of compound **161** (obtained as described in Step i, assumed 0.11 mmol) in THF (1.5 mL) was cooled to −78 °C then treated with freshly prepared LDA (513 mL of a 0.43 M solution, 0.22 mmol). Stirring was continued at −78 °C for 30 min then the reaction mixture was treated with a solution of phenylselenyl chloride (68.3 mL, of a 0.48 M solution in THF, 0.33 mmol). Stirring was continued for 15 min then the reaction mixture was warmed to 18 °C

over 30 min and quenched with NH_4Cl (2 mL of a saturated aqueous solution). The ensuing mixture was extracted with Et_2O (3 × 5 mL) and the combined organic fractions washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a *ca*. 3:1 mixture of the two diasteroisomeric forms of selenide **162**[72] as a clear, colourless oil. This material was used directly in Step iii.

Step iii: A solution of selenide **162** (obtained as described in Step ii, assumed 0.11 mmol) in THF/water/MeOH (4 mL of a 1:1:2 *v/v*/v mixture) was treated with $NaIO_4$ (121 mg, 0.54 mmol) and the ensuing mixture stirred at 18 °C for 1 h then diluted with CH_2Cl_2 (10 mL) and $Na_2S_2O_3$ (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash column chromatography (silica, 3:7 *v/v* EtOAc/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.5, 1:1 *v/v* EtOAc/hexane), the title dienone **115** (17.4 mg, 61% from compound **101**) as a clear, colourless oil. This material was often contaminated with varying amounts of the chromatographically inseparable precursor **161**. As a result, full characterization of compound **115** was carried out using samples prepared by Method 2 detailed immediately below.

Method 2: [*via* **methyl (2*S*,3a*R*,3b*R*,7a*S*)-4-[(dimethylamino)methyl]-2,3b-dimethyl-5-oxo-2,3,3a,3b,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalene-2-carboxylate (163)**]

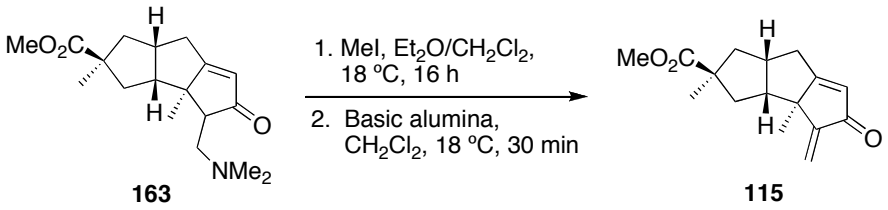


101 **163**

Step i: A solution of enone **101** (94 mg, 0.38 mmol) in THF (5 mL) maintained at −78 °C under a nitrogen atmosphere was treated, dropwise, with LiHMDS (566 mL of a 1.0 M solution in THF, 0.57 mmol) and the resulting mixture stirred at this temperature for 1 h. After this time Eschenmoser's salt (227 mg, 1.13 mmol) was added, in one portion, to the reaction mixture and this was then allowed to warm to 18 °C and stirred at this temperature for 16 h. The ensuing mixture was then quenched with HCl (20 ml of a 3.0 M aqueous solution) and after stirring for 5 min the aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with $NaHCO_3$ (20 mL of saturated aqueous solution) and brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the starting enone **101** (5 mg, 5% recovery) as a clear, colourless oil, which was identical, in all respects,

with authentic material. The aqueous layers obtained as described above were combined and basified to pH 14 using NaOH (4.0 M aqueous solution) and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give *amine* ***163*** (91 mg, 79% at 95% conversion) as a clear, colourless oil and as a single diastereoisomer of undetermined configuration at C4.

^{1}H NMR (300 MHz) δ 5.63 (d, *J* = 1.5 Hz, 1H), 3.65 (s, 3H), 2.75 (dd, *J* = 15.0 and 8.0 Hz, 1H), 2.68–2.44 (complex m, 3H), 2.40–2.24 (complex m, 5H), 2.20 (s, 6H), 1.47 (dd, *J* = 13.8 and 8.0 Hz, 1H), 1.34 (s, 3H), 1.27 (dd, *J* = 12.0 and 1.5 Hz, 1H), 1.13 (s, 3H).
IR ν_{max} 2957, 2923, 2851, 1729, 1700, 1635, 1465, 1373, 1198, 1165, 1093 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 305 ($M^{+\bullet}$, 20%), 260 (12), 201 (16), 200 (15), 170 (18), 141 (16), 77 (27), 58 (100).
HREIMS Found: $M^{+\bullet}$, 305.1992. $C_{18}H_{27}NO_3$ requires $M^{+\bullet}$, 305.1991.



163 **115**

Step ii: A solution of amine **163** (275 mg, 0.90 mmol) in Et_2O/CH_2Cl_2 (40 mL of a *v/v* 3:1 mixture) was treated with iodomethane (678 mL, 10.9 mmol), the resulting solution stirred at 18 °C for 16 h and then concentrated under reduced pressure. The ensuing white residue was dissolved in CH_2Cl_2 (5 mL) and the resulting solution treated with basic alumina (*ca*. 250 mg of 0.063–0.200 mesh and grade 1 activity material). The suspension thus formed was stirred at 18 °C for 30 min then concentrated under reduced pressure and the solid mass so obtained was dried under reduced pressure (*ca*. 6 mm Hg). The resulting solid was loaded onto the top of a flash chromatography column comprised of alumina and this was subsequently eluted with CH_2Cl_2. Concentration of the relevant fractions (R_f = 0.5, 1:1 *v/v* EtOAc/hexane) then afforded the title dienone **115** (179 mg, 76%) as a clear, colourless oil.

^{1}H NMR (600 MHz) δ 5.89 (s, 2H), 5.17 (s, 1H), 3.65 (s, 3H), 2.80 (dd, *J* = 7.5 and 3.9 Hz, 1H), 2.70 (m, 1H), 2.55 (dd, *J* = 6.3 and 4.2 Hz, 1H), 2.46–2.36 (complex m, 2H), 2.29 (ddd, *J* = 7.5, 3.6 and 0.6 Hz, 1H), 1.68–1.56 (complex m, 1H), 1.38 (s, 3H), 1.30 (t, *J* = 6.0 Hz, 1H), 1.17 (s, 3H).
^{13}C NMR (125 MHz) δ 197.6 (C), 189.3 (C), 177.9 (C), 153.6 (C), 123.5 (CH), 113.3 (CH_2), 54.9 (C), 52.1 (CH_3), 51.7 (C), 48.1 (CH), 46.4 (CH_2), 44.9 (CH), 37.0 (CH_2), 32.3 (CH_2), 24.5 (CH_3), 23.4 (CH_3).

IR ν_{max} 2962, 2925, 1727, 1701, 1622, 1466, 1374, 1307, 1256, 1196, 1165, 1094, 860 cm^{-1}.

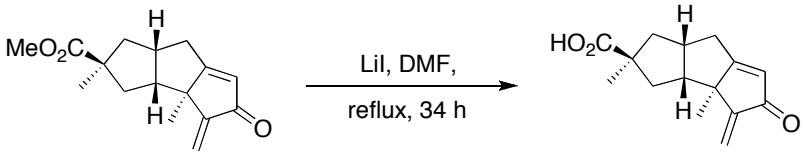
Mass spectrum (EI, 70 eV) *m/z* 260 ($M^{+\bullet}$, 65%), 247 (21), 232 (27), 202 (100), 201 (90), 200 (93), 132 (68), 121 (65), 91 (67).

HREIMS Found: $M^{+\bullet}$, 260.1417. $C_{16}H_{20}O_3$ requires $M^{+\bullet}$, 260.1412.

Optical Rotation $[\alpha]_D$ = +91 (*c* 0.3, $CHCl_3$) [lit.[72] $[\alpha]_D$ = +76.9 (*c* 0.4, $CHCl_3$) for 80% ee material].

The data presented above matched the equivalent spectral information reported in the literature.[72]

(2*S*,3a*R*,3b*S*,7a*S*)-2,3b-Dimethyl-4-methylene-5-oxo-2,3,3a,3b,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalene-2-carboxylic acid (136)



115 **136**

A solution of ester **115** (101 mg, 0.39 mmol) and anhydrous lithium iodide (780 mg, 5.83 mmol) in DMF (15 mL) was heated at reflux for 34 h then cooled and diluted with water (15 mL). The ensuing mixture was acidified with HCl (10% w/w aqueous solution) to pH 1–2 and then extracted with Et_2O (5 × 30 mL). The combined organic fractions were washed with water (10 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subject to flash column chromatography (silica, 1:1 *v/v* EtOAc/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5, 1:1 *v/v* EtOAc/hexane) afforded the starting ester **115** (23 mg, 22% recovery) as a clear, colourless oil. This material was identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.2, 1:1 *v/v* EtOAc/hexane) afforded the title acid **136** (69 mg, 73% at 78% conversion) as white needles, m.p. = 137–143 ºC (with decomposition) (lit.[64] m.p. = 113–115 °C).

^{1}H NMR (500 MHz) δ 5.90 (d, *J* = 0.9 Hz, 1H), 5.89 (s, 1H), 5.16 (s, 1H), 2.86–2.72 (complex m, 2H), 2.55 (ddd, *J* = 7.5, 4.2 and 0.9 Hz, 1H), 2.50–2.36 (complex m, 2H), 2.30 (m, 1H), 1.61 (dd, *J* = 7.5 and 4.8 Hz, 1H), 1.41 (s, 3H), 1.33 (t, *J* = 6.9 Hz, 1H), 1.17 (s, 3H) (signal due to carboxylic acid proton not observed).

^{13}C NMR (125 MHz) δ 197.7 (C), 189.3 (C), 183.7 (C), 153.5 (C), 123.5 (CH), 113.5 (CH_2), 54.7 (C), 51.7 (C), 48.1 (CH), 46.2 (CH_2), 44.8 (CH), 36.8 (CH_2), 32.3 (CH_2), 24.3 (CH_3), 23.4 (CH_3).

IR ν_{max} 2965, 1698, 1646, 1614, 1468, 1404, 1307, 1257, 1197, 1156, 941, 861 cm^{-1}.

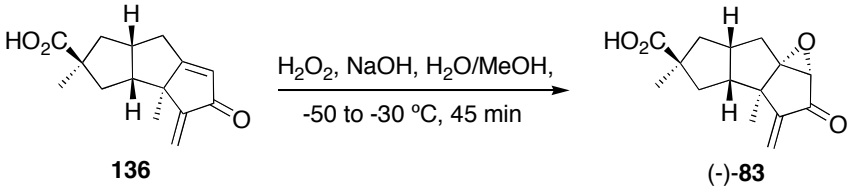
Mass spectrum (EI, 70 eV) *m/z* 246 ($M^{+\bullet}$, 100%), 218 (31), 201 (62), 200 (43), 132 (40), 91 (57).

HREIMS Found: $M^{+\bullet}$, 246.1256. $C_{15}H_{18}O_3$ requires $M^{+\bullet}$, 246.1256.

Optical Rotation $[\alpha]_D$ = +77 (*c* 0.7, $CHCl_3$) [lit.[71] $[\alpha]_D$ = +74 (*c* 0.4, $CHCl_3$)].

The data presented above matched the equivalent spectral information reported in the literature.[64,71,72]

(1a*S*,3a*R*,3b*R*,5*S*,6a*R*,7a*S*)-3a,5-Dimethyl-3-methylene-2-oxodecahydrocyclopenta-[4,5]pentaleno[1,6a-*b*]oxirene-5-carboxylic acid {(–)-complicatic acid [(-)-83]}



136 (-)-**83**

Following a procedure established by Ikegami *et al*.,[72] a solution of acid **136** (27 mg, 0.11 mmol) in MeOH (1.5 mL) was cooled to −50 °C and treated with hydrogen peroxide (110 μL of a 30% *w/v* aqueous solution, 0.33 mmol) then NaOH (330 μL of a 1.0 M aqueous solution, 0.33 mmol). The ensuing mixture was warmed to −36 °C over a period of 45 min, poured into NH_4Cl (5 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 5 mL). The combined organic fractions were washed with brine (2 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash column chromatography (silica, 1:1 *v/v* EtOAc/hexane elution) and concentration of the relevant fractions (R_f = 0.3, 1:1 *v/v* EtOAc/hexane) gave (–)-complicatic acid [(-)-**83**] (10 mg, 35%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.08 (s, 1H), 5.30 (s, 1H), 3.44 (s, 1H), 2.74 (m, 1H), 2.56 (ddd, *J* = 7.8, 4.5 and 3.9 Hz, 1H), 2.44 (m, 1H), 2.10–1.96 (complex m, 3H), 1.59 (dd, *J* = 7.8 and 5.4 Hz, 1H), 1.42 (s, 3H), 1.29 (t, *J* = 14.7 Hz, 1H), 1.19 (s, 3H) (signal due to carboxylic acid proton not observed).

^{13}C NMR (75 MHz) δ 197.7 (C), 183.7 (C), 152.6 (C), 120.5 (CH_2), 76.4 (C), 60.9 (CH), 53.2 (C), 49.6 (CH), 46.4 (C), 46.0 (CH_2), 39.2 (CH), 36.8 (CH_2), 29.7 (CH_2), 24.1 (CH_3), 17.4 (CH_3).

IR ν_{max} 2966, 1729, 1697, 1637, 1469, 1407, 1312, 1227, 1159, 1098, 944, 794, 750 cm^{-1}.

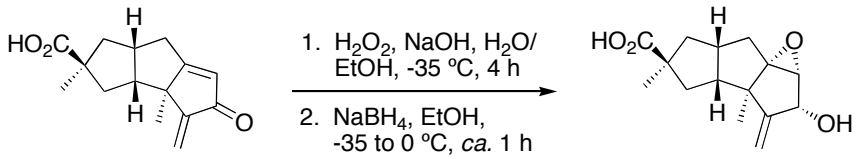
Mass spectrum (EI, 70 eV) *m/z* 262 ($M^{+\bullet}$, 4%), 205 (70), 159 (42), 105 (100), 77 (41).

HREIMS Found: $M^{+\bullet}$, 262.1215. $C_{15}H_{18}O_4$ requires $M^{+\bullet}$, 262.1205.

Optical Rotation $[\alpha]_D = -77$ (*c* 0.3, $CHCl_3$) [lit.[54] $[\alpha]_D = -79$ (*c* 1.1, $CHCl_3$)].

The data presented above matched the equivalent spectral information reported in the literature.[72]

(1a*R*,2*R*,3a*R*,3b*R*,5*S*,6a*R*,7a*S*)-2-Hydroxy-3a,5-dimethyl-3-methylenedecahydro-cyclopenta[4,5]pentaleno[1,6a-*b*]oxirene-5-carboxylic acid [(+)-hirsutic acid (82)]



136 (+)-**82**

Following a procedure established by Greene *et al*.,[71] a solution of acid **136** (25 mg, 0.10 mmol) in EtOH (1.5 mL) was cooled to -35 °C and treated with hydrogen peroxide (100 μL of a 30% *w/v* aqueous solution, 0.30 mmol) then NaOH (300 μL of a 1.0 M aqueous solution, 0.30 mmol). The reaction mixture was stirred at -35 °C for 4 h then EtOH (1.5 mL) and sodium borohydride (72 mg, 1.90 mmol) were added to the reaction mixture which was gradually warmed to 0 °C and then diluted with water (5 mL) followed by CH_2Cl_2 (5 mL). The ensuing mixture was then acidified with HCl (2% *w/v* aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash column chromatography (silica, 8:2:1 *v/v/v* hexane/EtOAc/acetic acid elution) afforded a white solid (R_f = 0.1, 1:1 *v/v* EtOAc/hexane). Recrystallization (CH_2Cl_2/cyclohexene) of this material afforded (+)-hirsutic acid (**82**) (12 mg, 46%) as white needles, m.p. = 168–171 ºC (lit.[72] m.p. = 170 ºC).

^{1}H NMR (600 MHz) δ 5.27 (s, 1H), 5.00 (s, 1H), 4.60 (s, 1H), 3.47 (s, 1H), 2.65 (m, 1H), 2.49 (dd, *J* = 6.0 and 3.9 Hz, 1H), 2.34 (m, 1H), 2.27 (m, 1H), 1.88 (m, 2H), 1.49 (dd, *J* = 6.6 and 4.5 Hz, 1H), 1.38 (s, 3H), 1.21 (m, 1H), 1.04 (s, 3H) (signals due to carboxylic acid and hydroxyl protons not observed).

^{13}C NMR (75 MHz) δ 183.4 (C), 158.4 (C), 111.9 (CH_2), 75.3 (C), 74.0 (CH), 63.6 (CH), 53.1 (C), 48.5 (C), 48.4 (CH), 46.3 (CH_2), 39.2 (CH), 36.5 (CH_2), 29.9 (CH_2), 24.1 (CH_3), 17.0 (CH_3).

IR ν_{max} 3397 (broad), 2965, 2071, 1698, 1468, 1438, 1405, 1378, 1310, 1260, 1217, 1168, 1099, 1066, 1029, 1000, 916, 888, 684 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 264 ($M^{+\bullet}$, 20%), 189 (100), 138 (90), 105 (67), 81 (60), 43 (63).

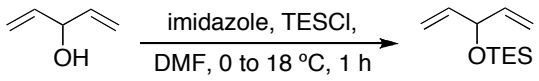
HREIMS Found: $M^{+\bullet}$, 264.1367. $C_{15}H_{20}O_4$ requires $M^{+\bullet}$, 264.1362.

Optical Rotation $[\alpha]_D$ = +113 (*c* 0.2, $CHCl_3$) [lit.[54] $[\alpha]_D$ = +116 (*c* 1.05, $CHCl_3$)].

The data presented above matched the equivalent spectral information reported in the literature.[64,71,72]

5.3 Experimental Procedures for Chapter Three

Triethyl[(1-vinylprop-2-en-1-yl)oxy]silane (200)



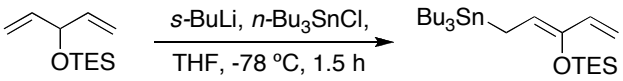
199 **200**

Following a procedure established by Oppolzer *et al.*,[123] a solution of 1,4-pentadiene-3-ol (**199**) (2.30 mL, 23.7 mmol) and imidazole (1.94 g, 28.5 mmol) in DMF (2 mL) was cooled to 0 ºC then chlorotriethylsilane (4.40 mL, 26.2 mmol) was added dropwise. The ensuing mixture was warmed to 18 ºC and stirred at this temperature for 1 h then poured into water (10 mL). The mixture was extracted with pentane (3 x 50 mL) and combined organic fractions were washed with water (2 x 20 mL) and brine (20 mL) then dried (Na_2SO_4), filtered and carefully concentrated under reduced pressure to give title silyl ether **200** (4.51 g, 96%) as a clear, colourless oil (R_f = 0.8, 1:1 *v/v* EtOAc/hexane). This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 5.83 (ddd, *J* = 17.2, 10.2 and 5.5 Hz, 2H), 5.22 (dt, *J* = 17.2 and 1.5 Hz, 2H), 5.07 (dt, *J* = 10.3 and 1.4 Hz, 2H), 4.60 (m, 2H), 0.96 (m, 9H), 0.62 (m, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[123]

Triethyl({1-[2-(tributylstannyl)ethyl]prop-2-en-1-yl}oxy)silane (194)



200 **194**

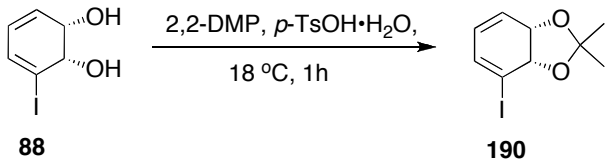
Following a procedure established by Fuchs *et al.*,[122] a solution of *s*-BuLi (13.7 mL of a 1.4 M solution in cyclohexane, 19.2 mmol) was added dropwise to a solution of silyl ether **200** (3.46 g, 17.4 mmol) in THF (11.5 mL) that had been cooled to -78 ºC. After the reaction mixture had been stirred at this temperature for 30 min tri-*n*-butyltin chloride (5.0 mL, 18.4 mmol) was added slowly. The reaction was allowed to stir for 1 h at -78 ºC then poured into NH_4Cl (20 mL of a saturated aqueous solution). The mixture was then extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic fractions were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a colourless oil. Purification of this material by

flash column chromatography (silica, hexane elution) and concentration of the appropriate fractions (R_f = 0.5, hexane) gave the title silyl enol ether **194** (6.87 g, 81%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.11 (dd, *J* = 17.0 and 10.7 Hz, 1H), 5.09 (d, *J* = 16.9 Hz, 1H), 4.94 (t, *J* = 9.3 Hz, 1H), 4.76 (d, *J* = 10.6 Hz, 1H), 1.75 (d, *J* = 9.2 Hz, 1H), 1.46 (m, 6H), 1.28 (m, 6H), 1.00 (m, 9H), 0.87 (m, 15H), 0.71 (m, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[122]

(3a*S*,7a*S*)-4-Iodo-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole (190)



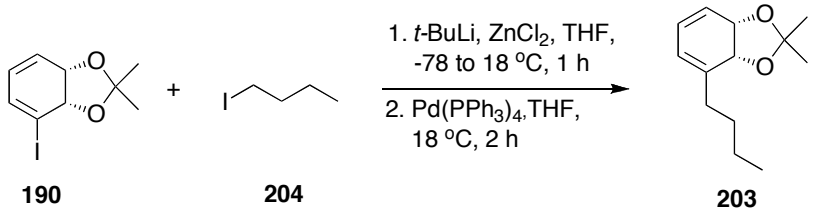
88 **190**

A solution of (1*S*,2*S*)-3-iodocyclohexa-3,5-diene-1,2-diol (**88**) (1.00 g, 4.20 mmol) in 2,2-dimethoxypropane (20 mL) was treated with *p*-TsOH•H_2O (*ca.* 30 mg, 0.16 mmol) then stirred at 18 ºC for 1 h before being quenched with triethylamine (0.5 mL) and concentrated under reduced pressure. The resultant brown residue was partitioned between water (20 mL) and Et_2O (50 mL) and the separated aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with NaOH (50 mL of a 2.0 M solution) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure (temp. = 30 ºC) to give title acetonide **190** (1.06 g, 91%) as a pale yellow oil (R_f = 0.6, 3:7 *v/v* EtOAc/hexane). This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 6.63 (d, *J* = 6.0 Hz, 1H), 6.03 (dd, *J* = 9.6 and 4.1 Hz, 1H), 5.76 (dd, *J* = 9.6 and 6.0 Hz, 1H), 4.74 (d, *J* = 8.5 Hz, 1H), 4.63 (dd, *J* = 8.5 and 4.1 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[194]

(3a*R*,7a*S*)-4-Butyl-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole (203)



190 **204** **203**

A solution of iodobutane (**204**) (80 μL, 0.70 mmol) in THF (3.5 mL) was cooled to -78 ºC then treated dropwise with *t*-BuLi (0.91 mL of a 1.7 M solution in pentane, 1.55 mmol). After stirring for 20 min, the reaction mixture was treated with $ZnCl_2$ (1.0 M solution of freshly fused $ZnCl_2$ in THF, 0.77 mL, 0.77 mmol) then warmed to 18 ºC and stirred at this temperature for 1 h to give a cloudy white solution. A solution of acetonide **190** (195 mg, 0.70 mmol) and $Pd(PPh_3)_4$ (81 mg, 0.07 mmol) in THF (3.5 mL) was added to the reaction mixture which was then stirred at 18 ºC for a further 2 h before being quenched by addition of water (15 mL) and Et_2O (30 mL). The separated aqueous phase was extracted with Et_2O (2 x 30 mL) and combined organic fractions were washed with water (20 mL), and brine (20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.4, 1:9 *v/v* EtOAc/hexane) gave *title compound **203*** (94.7 mg, 65%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.97 (dd, *J* = 9.8 and 5.7 Hz, 1H), 5.77 (dd, *J* = 9.8 and 3.9 Hz, 1H), 5.71 (d, *J* = 5.7 Hz, 1H), 4.65 (dd, *J* = 8.5 and 3.9 Hz, 1H), 4.53 (d, *J* = 8.5 Hz, 1H), 2.22 (m, 2H), 1.56–1.22 (complex m, 4H), 1.41 (s, 3H), 1.38 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz) δ 138.8 (C), 124.8 (CH), 122.4 (CH), 118.1 (CH), 105.2 (C), 73.5 (CH), 71.3 (CH), 33.3 (CH_2), 29.4 (CH_2), 26.9 (CH_3), 25.1 (CH_3), 22.5 (CH_2), 13.9 (CH_3).

IR ν_{max} 3046, 2958, 2931, 2872, 1466, 1378, 1368, 1236, 1217, 1159, 1051, 870 cm^{-1}.

Mass spectrum (EI, 70 eV) 208 ($M^{+\bullet}$, 3%), 205 (6), 193 [$(M - CH_3\bullet)^+$, 11%], 150 (60), 121 (22), 107 (100), 94 (75), 77 (40), 57 (38), 43 (47).

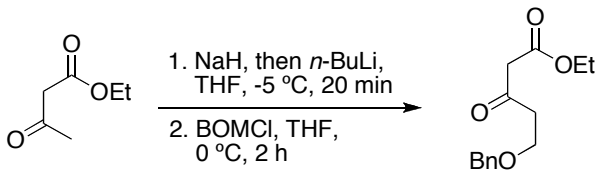
HREIMS Found: $M^{+\bullet}$, 208.1468. $C_{13}H_{20}O_2$ requires $M^{+\bullet}$, 208.1463;

Found: $[(M - CH_3\bullet)^+$, 193.1228. $C_{13}H_{20}O_2$ requires $[(M - CH_3\bullet)^+$, 193.1229.

Optical Rotation $[\alpha]_D$ = +125 (*c* 1.6, $CHCl_3$).

Ethyl 5-(benzyloxy)-3-oxopentanoate (210)

Method 1:



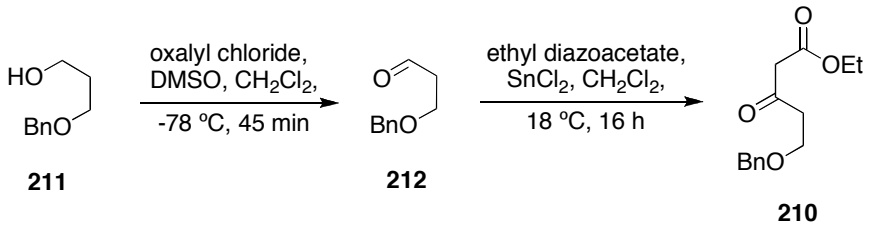
209 **210**

Following a procedure established by Taylor *et al.*,[129] a suspension of sodium hydride (1.10 g, 27.5 mmol) in THF (20 mL) maintained at -5 ºC was treated with ethyl acetoacetate (**209**) (3.20 mL, 25.1 mmol) in a dropwise manner. The reaction mixture was then stirred for 10 min at -5 ºC before being treated with *n*-BuLi (16.8 mL of a 1.6 M solution in THF, 26 mmol) and stirred at -5 ºC for a further 10 min. A solution of benzyl chloromethyl ether (*ca.* 60%, 8.74 mL, 37.7 mmol) in THF (10 mL) was then added and the mixture was stirred at 0 ºC for 2 h before being poured into NaCl (50 mL of a saturated aqueous solution). The mixture was acidified by addition of HCl (15 mL of a 10% aqueous solution) then extracted with Et_2O (3 x 25 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product as a yellow oil. Purification of tis material by flash column chromatography (silica, 1:9 → 3:7 *v/v* EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) gave the title compound **210** (2.89 g, 46%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.32 (m, 5H), 4.51 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.75 (t, *J* = 6.2 Hz, 2H), 3.48 (s, 2H), 2.83 (t, *J* = 6.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[130]

Method 2:



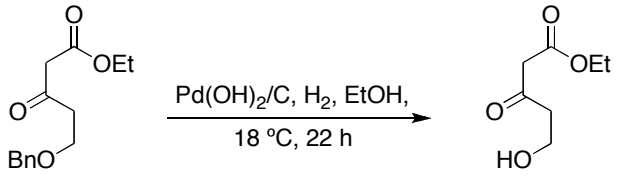
Following a procedure established by Heathcock *et al.*,[130] a solution of oxalyl chloride (3.10 mL, 35.5 mmol) in CH_2Cl_2 (50 mL) was cooled to -78 ºC and dimethyl sulfoxide (3.30 mL, 46.6 mmol) was added over 15 min. After stirring for a further 15 min a solution of 3-(benzyloxy)-1-propanol (**211**) (3.90 mL, 24.5 mmol) in CH_2Cl_2 (5 mL) maintained at -78 ºC was added *via* cannula. After 45 min triethylamine (13.0 mL, 93.3 mmol) was added and the ensuing mixture was warmed to 18 ºC and stirred at this temperature for 1 h. The reaction mixture was then poured into water (100 mL) and the separated aqueous phase was extracted with Et_2O (150 mL). The combined organic fractions were washed with water (2 x 50 mL) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give aldehyde **212** (4.12 g). This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 9.80 (t, *J* = 1.8 Hz, 1H), 7.34 (m, 5H), 4.54 (s, 2H), 3.82 (t, *J* = 6.1 Hz, 2H), 2.70 (td, *J* = 6.1 and 1.8 Hz, 2H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[195]

The crude aldehyde **212** (assumed 24.5 mmol), obtained as described immediately above, was dissolved in CH_2Cl_2 (60 mL) and the resuling solution was treated with $SnCl_2$ (884 mg, 4.66 mmol) then ethyl diazoacetate (2.7 mL, 25.7 mmol) over 25 min. The resulting exotherm was controlled by using a water bath maintained at 18 ºC. After 16 h the reaction mixture was poured into HCl (100 mL of a 1.0 M aqueous solution) and extracted with Et_2O (150 mL). The separated organic phase was washed with HCl (50 mL of a 1.0 M aqueous solution) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an orange oil. Purification by flash column chromatography (silica, 1:9 → 3:7 *v/v* EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) gave title compound **210** (3.37 g, 55% over two steps). This material was identical, in all respects, with material obtained *via* method 1.

Ethyl 5-hydroxy-3-oxopentanoate (213)



210 **213**

A solution of benzyl ether **210** (2.89 g, 11.5 mmol) in EtOH (50 mL) was treated with 20% palladium hydroxide on carbon (480 mg) and the resulting suspension was stirred at 18 °C under a hydrogen atmosphere (1 atm) for 22 h. The reaction mixture was filtered through a pad of Celite^{TM} (approx 5 cm thick) and the retained solids were washed with EtOH (2 x 20 mL) and EtOAc (2 x 20 mL). The combined filtrates were concentrated under reduced pressure to give the title alcohol **213** (1.76 g, 95%) as a clear, colourless oil (R_f = 0.2, 1:1 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 4.19 (q, *J* = 7.2 Hz, 2H), 3.86 (dt, *J* = 6.2 and 5.5 Hz, 2H), 3.48 (s, 2H), 2.80 (t, *J* = 5.5 Hz, 2H), 2.45 (br t, *J* = 6.2 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H).

The data presented above matched the equivalent spectral information reported in the literature.[129] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

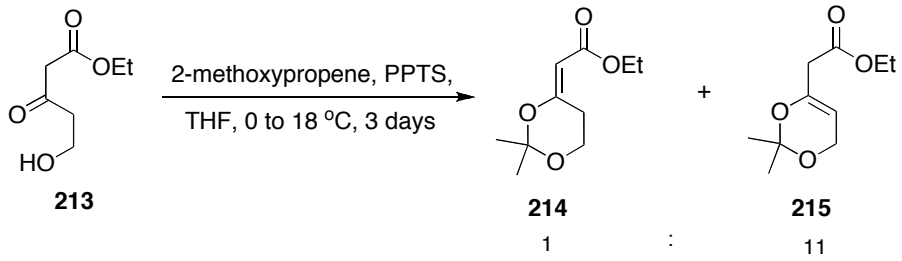
^{13}C NMR (75 MHz) δ 203.4 (C), 166.9 (C), 61.5 (CH_2), 57.5 (CH_2), 49.6 (CH_2), 44.9 (CH_2), 14.0 (CH_3).

IR ν_{max} 3418, 2982, 2939, 2904, 1740, 1713, 1467, 1446, 1410, 1369, 1316, 1265, 1198, 1148, 1095, 1031, 921, 850, 648, 588 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 160 ($M^{+\bullet}$, 2%), 115 (24), 88 (19), 73 (66), 69 (14), 60 (18), 55 (51), 43 (100).

HREIMS Found: $M^{+\bullet}$, 160.0738. $C_7H_{12}O_4$ requires $M^{+\bullet}$, 160.0736.

Ethyl 2-(2,2-dimethyl-1,3-dioxan-4-ylidene)acetate (214) and ethyl (2,2-dimethyl-4*H*-1,3-dioxin-6-yl)acetate (215)

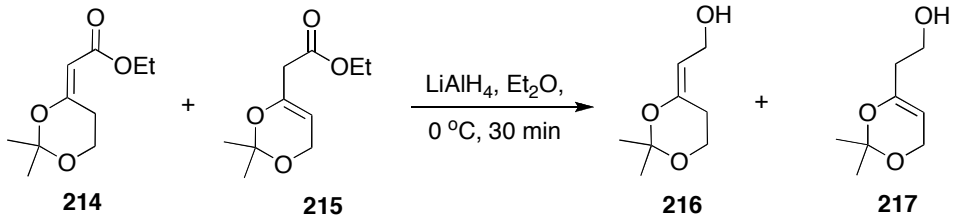


A procedure established by Funk *et al.*,[127] was adapted such that a solution of alcohol **213** (2.67 g, 16.7 mmol) in THF (55 mL) was cooled to 0 ºC then treated with 2-methoxypropene (97%, 5.0 mL, 50.6 mmol) and pyridinium *p*-toluenesulfonate (1.26 g, 5.01 mmol). The ensuing mixture was allowed to warm to 18 ºC and stirred at this temperature for 3 days after which time solid Na_2CO_3 (5 g) was added. The resulting mixture was stirred at 18 ºC for 1 h then filtered and the retained solids were washed with dry Et_2O (3 x 20 mL). The combined filtrates were concentrated under reduced pressure and the crude product was subjected to flash column chromatography (silica, 1:4 *v/v* EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.6, 3:7 *v/v* EtOAc/hexane) gave an inseparable mixture (1:11) of the title compounds **214** and **215** (2.48 g, 74%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ (**215**, major isomer) 4.79 (t, *J* = 2.7 Hz, 1H), 4.21 (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.04 (m, 2H), 1.46 (s, 6H), 1.25 (t, *J* = 7.2 Hz, 3H); (**214**, minor isomer) 5.32 (t, *J* = 1.2 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.07 (dd, *J* = 6.3 and 1.5 Hz, 2H), 1.48 (s, 6H), 1.26 (t, *J* = 7.2 Hz, 3H).

The ^{1}H NMR spectral data derived from compound **215** were in agreement with those reported in the literature.[127]

2-(2,2-Dimethyl-1,3-dioxan-4-ylidene)ethanol (216) and 2-(2,2-dimethyl-4*H*-1,3-dioxin-6-yl)ethanol (217)



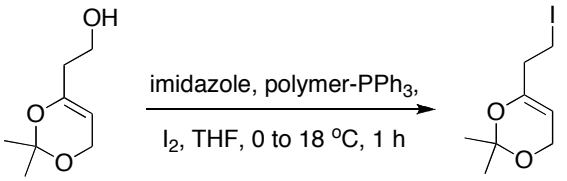
214 **215** **216** **217**

Following a procedure established by Funk *et al.*,[127] a suspension of $LiAlH_4$ (708 mg, 18.6 mmol) in Et_2O (115 mL) was cooled to 0 ºC and a solution of esters **214** and **215** (2.48 g, 12.4 mmol) in Et_2O (10 mL) was then added dropwise over 10 min. The ensuing mixture was stirred at 0 ºC for 30 min then quenched, successively, with water (1 mL), NaOH (1.1 mL of a 10% *w/v* aqueous solution) and water (2.2 mL). The resulting suspension was filtered, the retained solids washed with Et_2O (3 x 50 mL) and then the combined filtrates were concentrated under reduced pressure. Purification of the ensuing yellow oil by flash column chromatography (silica, 2:3 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 1:1 *v/v* EtOAc/hexane) gave the title alcohol **217** (1.76 g, 90%) as a clear, colourless oil. *Alcohol **216*** was never isolated in significant quantities.

^{1}H NMR (300 MHz) δ 4.71 (t, *J* = 2.6 Hz, 1H), 4.19 (m, 2H), 3.74 (q, *J* = 5.9 Hz, 2H), 2.29 (t, *J* = 6.0 Hz, 2H), 1.83 (t, *J* = 5.9 Hz, 1H), 1.45 (s, 6H) (OH proton resonances not observed).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[127]

6-(2-Iodoethyl)-2,2-dimethyl-4*H*-1,3-dioxine (207)



217 **207**

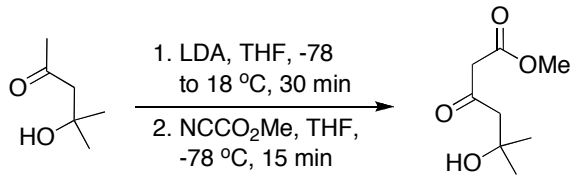
A procedure established by Funk *et al.*,[127] was adapted such that a solution of alcohol **217** (208 mg, 1.31 mmol) in THF (12.5 mL) was cooled to 0 ºC and treated with imidazole (202 mg, 2.96 mmol), polymer bound triphenylphosphine (3 mmol/g, 878 mg, 2.63 mmol) and molecular iodine (669 mg, 2.63 mmol). The ensuing mixture was allowed to warm to 18 ºC and stirred at

this temperature for a further 1 h then poured into $Na_2S_2O_3$ (10 mL of a 10% *w/v* aqueous solution). The resulting mixture was extracted with Et_2O (3 x 30 mL) and the combined organic fractions were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure (water bath kept at 5–10 ºC, protect from light) to afford iodo-dioxin **207** (255 mg, 73%) as an unstable colourless oil (R_f = 0.7, 1:1 *v/v* EtOAc/hexane). This material was used immediatly in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 4.71 (t, *J* = 2.6 Hz, 1H), 4.18 (m, 2H), 3.26 (t, *J* = 7.1 Hz, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 1.46 (s, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[127]

Methyl 5-hydroxy-5-methyl-3-oxohexanoate (219)



218 **219**

A solution of di*iso*propylamine (3.0 mL, 21.4 mmol) in THF (20 mL) was cooled to -78 ºC then treated with *n*-BuLi (12.5 mL of a 1.6 M solution in hexanes, 20.0 mmol) in a dropwise manner. After 15 min 4-hydroxy-4-methyl-2-pentanone (**218**) (1.1 mL, 8.82 mmol) was added dropwise and the ensuing reaction mixture was stirred at -78 ºC for 10 min then warmed to 18 ºC and stirred for a further 15 min at this temperature. The resultant solution was re-cooled to -78 ºC then treated with methyl cyanoformate (720 μL, 9.07 mmol) in THF (20 mL) and stirred for 15 min before being diluted with HCl to a pH of <1 (3.0 M aqueous solution, *ca.* 10 mL). The ensuing mixture was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow liquid. Purification of this material by flash column chromatography (silica, 3:7 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.2, 1:1 *v/v* EtOAc/hexane) gave the *title keto-alcohol **219*** (789 mg, 50%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 3.74 (s, 3H), 3.48 (s, 2H), 2.73 (s, 2H), 1.27 (s, 6H) (OH proton resonances not observed).

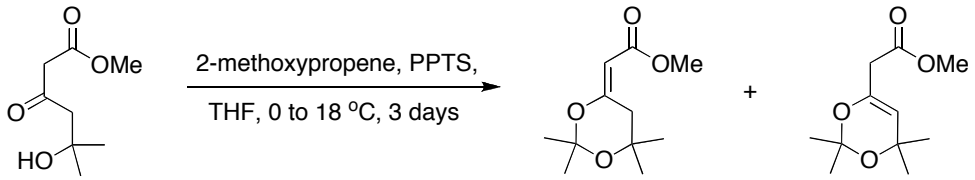
^{13}C NMR (75 MHz) δ 204.3 (C), 167.3 (C), 69.7 (C), 53.6 (CH_2), 52.5 (CH_3), 50.3 (CH_2), 29.3 (CH_3).

IR ν_{max} 3511, 2974, 1746, 1708, 1653, 1631, 1438, 1378, 1325, 1258, 1171, 1073, 1018 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 159 [$(M - CH_3\cdot)^+$, 10%], 127 (16), 116 (16), 101 (16), 83 (25), 59 (58), 55 (25), 43 (100).

HREIMS Found: $(M - CH_3\cdot)^+$, 159.0660. $C_8H_{14}O_4$ requires $(M - CH_3\cdot)^+$, 159.0657.

Methyl 2-(2,2,6,6-tetramethyl-1,3-dioxan-4-ylidene)acetate (221) and methyl (2,2,4,4-tetramethyl-4*H*-1,3-dioxin-6-yl)acetate (222)



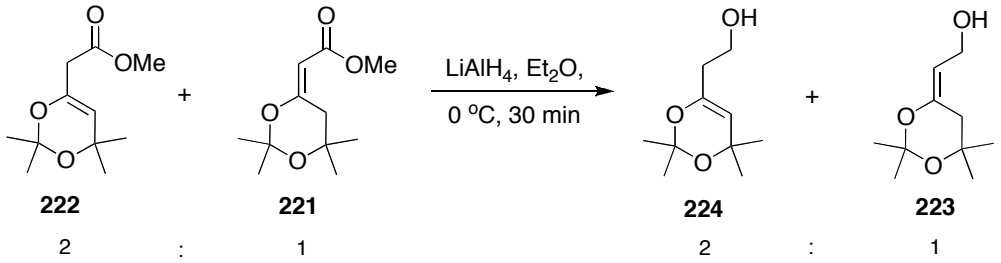
219 **221** : **222**

1 2

A solution of alcohol **219** (2.37 g, 13.6 mmol) in THF (45 mL) was cooled to 0 ºC and treated with 2-methoxypropene (97%, 4.5 mL, 42.9 mmol) and pyridinium *p*-toluenesulfonate (1.03 g, 4.09 mmol). The ensuing mixture was allowed to warm to 18 ºC and stirred at this temperature for 3 days after which time solid Na_2CO_3 (5 g) was added. The resulting mixture was stirred at 18 ºC for 1 h then filtered and the retained solids washed with dry Et_2O (3 x 20 mL). The combined filtrates were concentrated under reduced pressure and the crude product was subjected to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.5, 3:7 *v/v* EtOAc/hexane) gave an inseparable mixture (1:2) of the *title compounds **221*** and ***222*** (2.02 g, 69%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ (**222**, major isomer) 4.85 (s, 1H), 3.70 (s, 3H), 3.05 (s, 2H), 1.48 (s, 6H), 1.31 (s, 6H); (**221**, minor isomer) 5.37 (s, 1H), 3.66 (s, 3H), 3.23 (s, 2H), 1.49 (s, 6H), 1.31 (s, 6H).

2-(2,2,4,4-Tetramethyl-4*H*-1,3-dioxin-6-yl)ethanol (224) and 2-(2,2,6,6-tetramethyl-1,3-dioxan-4-ylidene)ethanol (223)



A suspension of $LiAlH_4$ (461 mg, 12.1 mmol) in Et_2O (90 mL) was cooled to 0 ºC and a solution of esters **221** and **222** (2.00 g, 9.34 mmol) in Et_2O (5 mL) was added dropwise over 10 min. The ensuing reaction mixture was stirred at 0 ºC for 30 min then quenched, successively, with water (475 μL), NaOH (735 μL of a 10% *w/v* aqueous solution) and water (1.4 mL). The resulting suspension was filtered, the retained solids washed with Et_2O (3 x 50 mL) then the combined filtrates were concentrated under reduced pressure. The ensuing yellow oil was subjected to flash column chromatography (silica, 3:7 → 1:1 *v/v* EtOAc/hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded *title alcohol **224*** (1.15 g, 66%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 4.77 (m, 1H), 3.74 (q, *J* = 5.9 Hz, 2H), 2.28 (t, *J* = 4.6 Hz, 2H), 1.75 (t, *J* = 5.9 Hz, 1H), 1.48 (s, 6H), 1.29 (s, 6H) (OH proton resonances not observed).
^{13}C NMR (75 MHz) δ 146.4 (C), 106.6 (CH), 99.2 (C), 71.0 (C), 60.4 (CH_2), 37.1 (CH_2), 30.4 (CH_3), 26.8 (CH_3).
IR ν_{max} 3411, 2974, 2917, 2849, 1693, 1379, 1368, 1344, 1243, 1215, 1201, 1152, 1105, 1044, 1018, 976, 910, 872, 733 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 187 [$(M + H)^+$, 5%], 169 (5), 128 (6), 111 (18), 95 (9), 83 (84), 73 (25), 59 (32), 55 (42), 43 (100).
HREIMS Found: $(M + H)^+$, 187.1337. $C_{10}H_{18}O_3$ requires $(M + H)^+$, 187.1334.

Concentration of fraction B [R_f = 0.1(5), 3:7 *v/v* EtOAc/hexane] gave the *title alcohol **223*** (527 mg, 30%) as a clear, colourless oil.

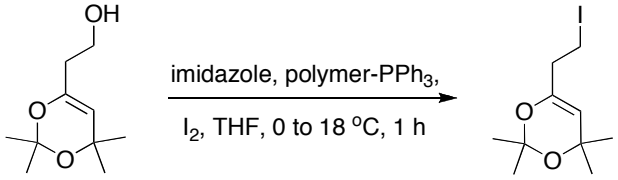
^{1}H NMR (300 MHz) δ 5.21 (tt, *J* = 7.9 and 1.5 Hz, 1H), 4.09 (d, *J* = 7.9 Hz, 2H), 2.52 (s, 2H), 1.75 (br s, 1H), 1.45 (s, 6H), 1.29 (s, 6H).

^{13}C NMR (75 MHz) δ 151.2 (C), 105.6 (CH), 101.0 (C), 71.5 (C), 57.6 (CH_2), 34.6 (CH_2), 30.0 (CH_3), 29.5 (CH_3).

IR ν_{max} 3409, 2976, 2936, 2876, 1678, 1380, 1369, 1306, 1241, 1202, 1150, 1097, 1018, 987, 929, 875 cm^{-1}.

HREIMS (ES, +ve mode) Found: $(M + Na)^+$, 209.1152. $C_{10}H_{18}O_3$ requires $(M + Na)^+$, 209.1154.

6-(2-Iodoethyl)-2,2,4,4-tetramethyl-4*H*-1,3-dioxine (208)



224 **208**

A solution of alcohol **224** (169 mg, 0.91 mmol) in THF (10 mL) was cooled to 0 ºC and treated with imidazole (154 mg 2.26 mmol), polymer bound triphenylphosphine (3 mmol/g, 603 mg, 1.81 mmol) and iodine (460 mg, 1.81 mmol). The ensuing mixture was allowed to warm to 18 ºC and stirred for a futher 1 h then poured into $Na_2S_2O_3$ (10 mL of a 10% *w/v* aqueous solution). The resulting mixture was extracted with Et_2O (3 x 30 mL) and the combined organic fractions were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure (water bath kept at 5–10 ºC, protect from light) to give *iodo-dioxin* ***208*** (223 mg, 83%) as an unstable colourless oil (R_f = 0.6, 3:7 *v/v* EtOAc/hexane). This material was used immediatly in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 4.75 (t, *J* = 0.7 Hz, 1H), 3.26 (t, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 1.48 (s, 6H), 1.30 (s, 6H).

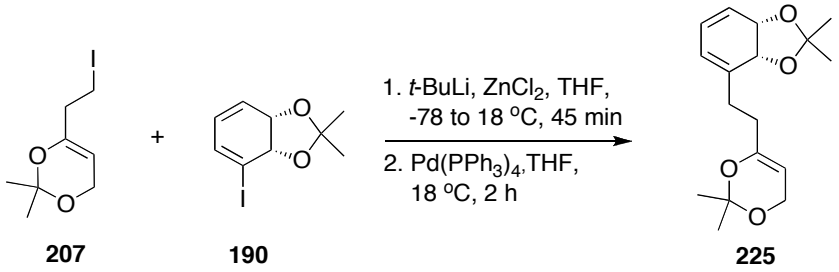
^{13}C NMR (75 MHz) δ 146.6 (C), 106.7 (CH), 99.2 (C), 71.0 (C), 38.2 (CH_2), 30.2 (CH_3), 27.0 (CH_3), 2.5 (CH_2).

IR ν_{max} 2971, 2928, 1705, 1618, 1463, 1436, 1368, 1378, 1347, 1314, 1260, 1241, 1217, 1200, 1171, 1103, 1071, 1023, 976, 907, 868, 806 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 239 {$[M + H - (CH_3)_2CO]^+$, 74%}, 183 (95), 155 (100), 83 (64), 71 (19), 59 (38), 55 (60), 43 (55).

HREIMS Found: $[M + H - (CH_3)_2CO]^+$, 238.9937. $C_{10}H_{17}O_2{}^{127}I$ requires $[M + H - (CH_3)_2CO]^+$, 238.9933.

(3a*R*,7a*S*)-4-[2-(2,2-Dimethyl-4*H*-1,3-dioxin-6-yl)ethyl]-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole (225)

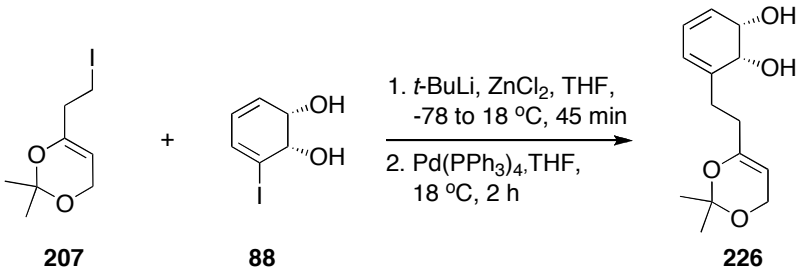


207 **190** **225**

A solution of iodo-dioxin **207** (255 mg, 0.95 mmol) in THF (5 mL) was treated with $ZnCl_2$ (1.05 mL of a 1.0 M solution of freshly fused $ZnCl_2$ in THF, 1.05 mmol) then cooled to -78 ºC. *t*-BuLi (1.7 mL of a 1.7 M solution in pentane, 2.89 mmol) was added dropwise and the resulting solution allowed to stir at -78 ºC for 15 min then warmed to 18 ºC and stirred at this temperature for 30 min. This solution was then added, *via* cannula, to a solution of vinyl iodide **190** (175 mg, 0.63 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (5 mL) and the ensuing mixture stirred for a further 2 h at 18 ºC then quenched by addition of water (15 mL) and Et_2O (30 mL). The separated aqueous phase was extracted with Et_2O (2 x 30 mL) and the combined organic fractions were washed with water (20 mL) and brine (20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 1:9 *v/v* EtOAc/hexane) gave the *title compound **225*** (53.3 mg, 29%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.98 (dd, *J* = 9.6 and 5.5 Hz, 1H), 5.80 (dd, *J* = 9.6 and 3.7 Hz, 1H), 5.73 (d, *J* = 5.5 Hz, 1H), 4.66 (dd, *J* = 8.6 and 3.7 Hz, 1H), 4.63 (t, *J* = 2.6 Hz, 1H), 4.55 (d, *J* = 8.6 Hz, 1H), 4.18 (m, 2H), 2.41 (m, 2H), 2.26 (m, 2H), 1.44 (s, 6H), 1.41 (s, 3H), 1.39 (s, 3H).
^{13}C NMR (75 MHz) δ 150.7 (C), 137.5 (C), 124.7 (CH), 122.8 (CH), 118.6 (CH), 105.3 (C), 98.6 (C), 93.9 (CH), 73.4 (CH), 71.3 (CH), 59.2 (CH_2), 31.6 (CH_2), 30.6 (CH_2), 26.9 (CH_3), 25.1 (CH_3), 24.5 (CH_3), 24.3 (CH_3).
IR ν_{max} 3043, 2990, 2933, 2840, 1683, 1455, 1370, 1333, 1229, 1204, 1139, 1092, 1024, 978, 852, 709 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 292 ($M^{+\bullet}$, 12%), 219 (15), 176 (72), 159 (69), 147 (47), 133 (31), 121 (80), 107 (107), 91 (45), 77(48), 55 (97), 43 (85).
HREIMS Found: $M^{+\bullet}$, 292.1677. $C_{17}H_{24}O_4$ requires $M^{+\bullet}$, 292.1675.
Optical Rotation $[\alpha]_D$ = +93 (*c* 0.4, $CHCl_3$).

(1*S*,2*R*)-3-[2-(2,2-Dimethyl-4*H*-1,3-dioxin-6-yl)ethyl]cyclohexa-3,5-diene-1,2-diol (226)

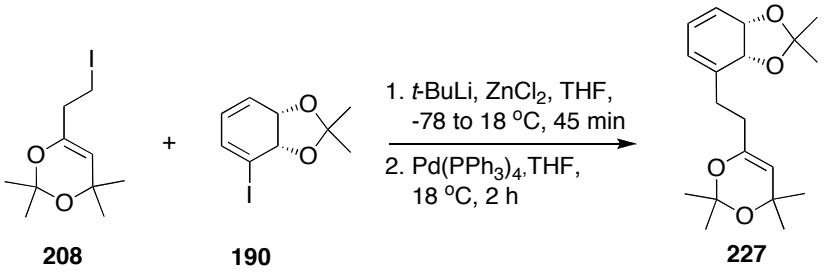


207 **88** **226**

A solution of iodo-dioxin **207** (281 mg, 1.05 mmol) in THF (5 mL) was treated with $ZnCl_2$ (1.15 mL of a 1.0 M solution of freshly fused $ZnCl_2$ in THF, 1.15 mmol) then cooled to -78 ºC. *t*-BuLi (1.8 mL of a 1.7 M solution in pentane, 3.06 mmol) was added dropwise and the resultant solution was allowed to stir at -78 ºC for 15 min then warmed to 18 ºC and stirred at this temperature for 30 min. This solution was then added, *via* cannula, to a mixture of diol **88** (166 mg, 0.697 mmol) and $Pd(PPh_3)_4$ (80 mg, 0.092 mmol). The ensuing mixture was stirred for 2 h then quenched by addition of half brine (15 mL) and Et_2O (30 mL). The separated aqueous phase was extracted with Et_2O (4 x 30 mL) and the combined organic fractions were then washed with brine (20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica deactivated with 10% *w/w* water, 3:7 → 1:1 *v/v* EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.1, 3:7 *v/v* EtOAc/hexane) gave the *title compound* ***226*** (42.2 mg, 24%) as an unstable colourless oil. This material was used immediately in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 5.92 (ddd, *J* = 9.7, 5.0 and 1.5 Hz, 1H), 5.79 (dd, *J* = 9.7 and 3.4 Hz, 1H), 5.72 (d, *J* = 5.0 Hz, 1H), 4.63 (t, *J* = 2.6 Hz, 1H), 4.30 (br s, 1H), 4.17 (m, 2H), 4.05 (d, *J* = 6.0 Hz, 1H), 2.42 (m, 2H), 2.24 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H) (OH proton resonances not observed).

(3a*R*,7a*S*)-2,2-Dimethyl-4-[2-(2,2,4,4-tetramethyl-4*H*-1,3-dioxin-6-yl)ethyl]-3a,7a -dihydro-1,3-benzodioxole (227)



208 **190** **227**

A solution of iodo-dioxin **208** (223 mg, 0.75 mmol) in THF (4 mL) was cooled to -78 ºC then treated dropwise with *t*-BuLi (0.97 mL of a 1.7 M solution in pentane, 1.65 mmol). After stirring at this temperature for 20 min the reaction mixture was treated with $ZnCl_2$ (830 μL of a 1.0 M solution of freshly fused $ZnCl_2$ in THF, 0.83 mmol) then warmed to 18 ºC and stirred at this temperature for 1 h to give a cloudy white solution. A solution of acetonide **190** (140 mg, 0.50 mmol) and $Pd(PPh_3)_4$ (78 mg, 0.07 mmol) in THF (3.5 mL) was then added and the resulting mixture was stirred for a futher 2 h then quenched by addition of water (15 mL) and Et_2O (30 mL). The separated aqueous phase was extracted with Et_2O (2 x 30 mL) and combined organic fractions were washed with water (20 mL) and brine (20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the resulting yellow oil by flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 1:9 *v/v* EtOAc/hexane) gave *title compound **227*** (69.2 mg, 43%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.96 (dd, *J* = 9.8 and 5.6 Hz, 1H), 5.78 (dd, *J* = 9.8 and 3.9 Hz, 1H), 5.73 (d, *J* = 5.6 Hz, 1H), 4.66 (m, 2H), 4.53 (d, *J* = 8.9 Hz, 1H), 2.40 (m, 2H), 2.21 (m, 2H), 1.45 (s, 6H), 1.41 (s, 3H), 1.39 (s, 3H), 1.26 (s, 6H).

^{13}C NMR (75 MHz) δ 148.4 (C), 137.5 (C), 124.5 (CH), 122.9 (CH), 118.7 (CH), 105.3 (C), 104.7 (CH), 98.9 (C), 73.4 (CH), 71.4 (CH), 70.9 (C), 31.6 (CH_2), 30.6 (CH_2), 30.4 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.1 (CH_3).

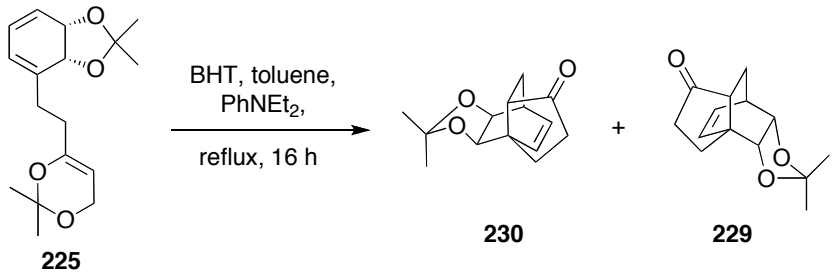
IR ν_{max} 2989, 2934, 1683, 1442, 1378, 1368, 1347, 1242, 1203, 1156, 1105, 1019, 977, 871, 816, 778, 720 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 262 {[M – $(CH_3)_2CO]^{+\bullet}$, 5%}, 204 (41), 189 (15), 149 (47), 121 (41), 104 (71), 91 (31), 83 (100), 77 (35), 55 (75), 43 (69).

HREIMS Found: [M – $(CH_3)_2CO]^{+\bullet}$, 262.1566. $C_{19}H_{28}O_4$ requires [M – $(CH_3)_2CO]^{+\bullet}$, 262.1569.

Optical Rotation $[\alpha]_D$ = +101 (*c* 1.3, $CHCl_3$).

(3a*S*,4*S*,5a*S*,8a*S*,8b*R*)-2,2-Dimethylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (230) and (3a*S*,4*R*,5a*R*,8a*R*,8b*R*)-2,2-dimethylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (229)



225 **230** **229**

A mixture of dioxin **225** (6.3 mg, 0.02 mmol), BHT (1.9 mg, 0.01 mmol) and *N,N*-diethylaniline (50 μL, 0.31 mmol) in toluene (5 mL) was heated at reflux for 16 h then cooled and concentrated under reduced pressure. Purification of the ensuing light-yellow oil by flash column chromatography (silica, 1:4 → 2:3 *v/v* EtOAc/hexane gradient elution) afforded two fractions, A and B.

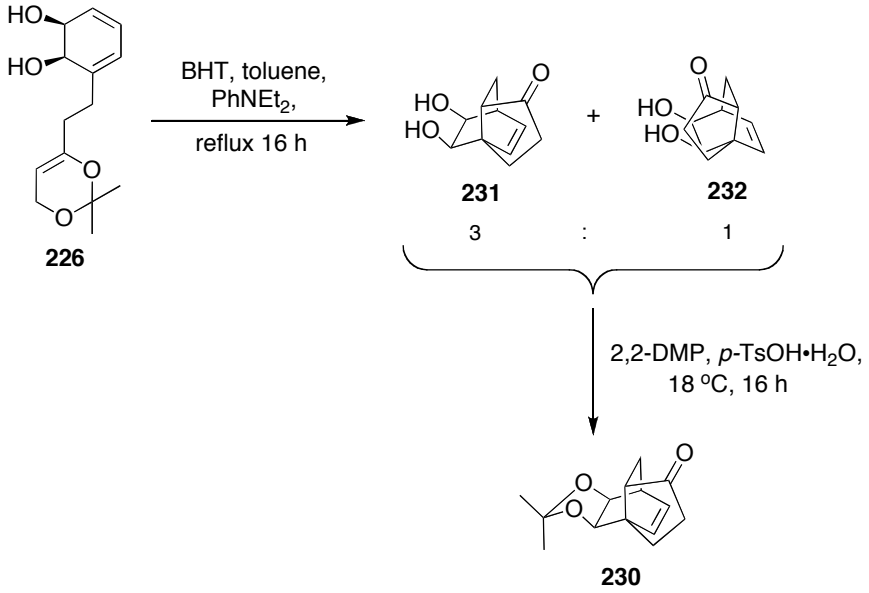
Concentration of fraction A (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded the *title syn-adduct* ***230*** (2.2 mg, 35%) as a white crystalline solid, m.p. = 93–96 ºC.

^{1}H NMR (300 MHz) δ 6.35 (dd, *J* = 8.0 and 6.8 Hz, 1H), 5.81 (dd, *J* = 8.0 and 1.0 Hz, 1H), 4.08 (ddd, *J* = 8.0, 4.2 and 0.7 Hz, 1H), 5.81 (dd, *J* = 8.0 Hz, 1H), 2.84 (m, 1H), 2.66 (ddd, *J* = 10.0, 6.1 and 1.7 Hz, 1H), 2.49–2.36 (m, 1H), 2.23–1.95 (complex m, 4H), 1.49 (s, 3H), 1.40 (ddd, *J* = 6.1, 2.4 and 1.0 Hz, 1H), 1.35 (s, 3H).
^{13}C NMR (75 MHz) δ 217.8 (C), 137.0 (CH), 133.7 (CH), 112.3 (C), 77.1 (CH), 75.0 (CH), 47.7 (C), 45.9 (CH), 36.2 (CH_2), 35.0 (CH), 26.5 (CH_3), 25.2 (CH_2), 24.4 (CH_3), 22.8 (CH_2).
IR ν_{max} 2993, 2965, 2932, 2861, 1739, 1450, 1376, 1268, 1209, 1144, 1110, 1069, 1058, 1016, 872, 723 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 234 ($M^{+\bullet}$, 4%), 219 [$(M - CH_3\bullet)^+$, 50], 205 (37), 176 (85), 159 (71), 147 (99), 133 (98), 120 (78), 105 (95), 100 (97), 91 (100), 77 (55), 65 (37), 55 (45), 43 (79).
HREIMS Found: $(M - CH_3\bullet)^+$, 219.1021. $C_{14}H_{18}O_3$ requires $(M - CH_3\bullet)^+$, 219.1021.
Elemental Analysis Found: C, 71.50; H, 7.75. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%.
Optical Rotation $[\alpha]_D$ = +128 (*c* 1.04, $CHCl_3$).

Concentration of fraction B (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded the *title anti-adduct* ***229*** (2.9 mg, 46%) as a white crystalline solid, m.p. = 131–134 ºC.

^{1}H NMR (300 MHz) δ 6.29 (t, *J* = 7.3 Hz, 1H), 5.74 (d, *J* = 8.3 Hz, 1H), 4.28 (ddd, *J* = 7.1, 2.7 and 1.0 Hz, 1H), 4.23 (dd, *J* = 7.1 and 1.0 Hz, 1H), 2.88 (m, 1H), 2.51–2.18 (m, 3H), 1.99–1.88 (m, 2H), 1.65–1.47 (m, 2H), 1.33 (s, 3H), 1.28 (s, 3H).
^{13}C NMR (75 MHz) δ 215.2 (C), 135.7 (CH), 130.7 (CH), 109.1 (C), 83.3 (CH), 79.5 (CH), 50.1 (CH), 47.5 (C), 36.9 (CH_2), 35.7 (CH), 28.4 (CH_2), 25.5 (CH_3), 24.9 (CH_3), 23.5 (CH_2).
IR ν_{max} 2986, 2934, 2886, 2865, 1742, 1455, 1378, 1368, 1207, 1142, 1068, 1058, 883, 745, 717 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 234 ($M^{+\bullet}$, 12%), 219 (70), 176 (91), 147 (98), 133 (100), 120 (74), 105 (88), 100 (77), 91 (99), 85 (52), 77 (45), 55 (36), 43 (75).
HREIMS Found: $M^{+\bullet}$, 234.1256. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256.
Elemental Analysis Found: C, 71.58; H, 7.73. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%.
Optical Rotation $[\alpha]_D$ = -102 (*c* 1.2, $CHCl_3$).

(3a*S*,4*S*,5a*S*,8a*S*,8b*R*)-2,2-Dimethylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (230) [*via* **(3a*S*,6*S*,7a*S*,8*S*,9*R*)-8,9-dihydroxy-2,3,7,7a-tetrahydro-3a,6-ethanoinden-1(6*H*)-one (231) and (3a*S*,6*S*,7a*R*,8*S*,9*R*)-8,9-dihydroxy-2,3,7,7a-tetrahydro-3a,6-ethanoinden-1(6*H*)-one (232)**]



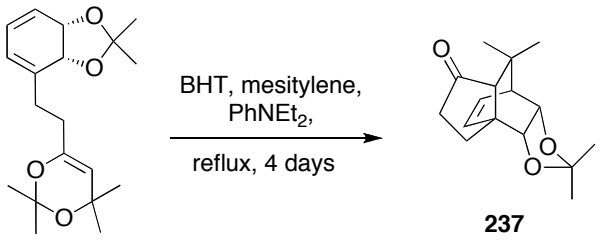
A mixture of dioxin **226** (20.0 mg, 0.08 mmol), BHT (2.0 mg, 0.01 mmol) and *N,N*-diethylaniline (100 μL, 0.63 mmol) in toluene (10 mL) was heated at reflux for 16 h then cooled and concentrated under reduced pressure. Purification of the ensuing light-yellow oil by

flash column chromatography (silica, 1:1 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) gave an inseparable (3:1) mixture of two Diels-Alder adducts tentatively assigned as *title compounds **231** and **232*** (12.1 mg, 78%).

^{1}H NMR (300 MHz) δ (**231**, major isomer) 6.32 (dd, *J* = 8.2 and 6.6 Hz, 1H), 5.83 (d, *J* = 8.2 Hz, 1H), 3.73 (m, 1H), 3.61 (m, 1H), 2.77–1.92 (complex m, 7H), 1.41 (m, 1H) (OH proton resonances not observed); (**323**, minor isomer) 6.23 (d, *J* = 8.2 Hz, 1H), 6.13 (dd, *J* = 8.2 and 6.3 Hz, 1H), 3.65 (m, 1H), 3.58 (m, 1H), 2.77–1.92 (complex m, 7H), 1.41 (m, 1H) (OH proton resonances not observed).

A solution of diols **231** and **232** (12.1 mg, 0.06 mmol) and 2,2-dimethoxypropane (115 μL, 0.93 mmol) in CH_2Cl_2 (1 mL) was treated with *p*-TsOH•H_2O (5 mg, 0.03 mmol) and the resulting solution stirred at 18 º C for 16 h before being quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and diluted with Et_2O (10 mL). The separated aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic phases were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 *v/v* EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) afforded *syn*-adduct **230** (10.4 mg, 71%) as a white crystalline solid. This material was identical, in all respects, with authentic material.

(3a*S*,4*S*,5a*R*,8a*R*,8b*R*)-2,2,5,5-Tetramethylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (237)



227 **237**

A mixture of dioxin **227** (49.9 mg, 0.16 mmol), BHT (3.8 mg, 0.02 mmol) and *N,N*-diethylaniline (350 μL, 2.20 mmol) in mesitylene (35 mL) was heated at reflux for 4 days then cooled and concentrated under reduced pressure. Purification of the ensuing light-yellow oil by flash column chromatography (silica, 1:4 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded *compound **237*** (13.1 mg, 32%) as a white crystalline solid, m.p. = 101–104 ºC.

^{1}H NMR (300 MHz) δ 6.31 (t, *J* = 7.3 Hz, 1H), 5.81 (d, *J* = 8.0 Hz, 1H), 4.62 (ddd, *J* = 7.1, 2.9 and 1.0 Hz, 1H), 4.18 (dd, *J* = 7.1 and 1.0 Hz, 1H), 2.47 (ddd, *J* = 6.6, 2.9 and 1.0 Hz, 1H), 2.36–2.22 (m, 3H), 1.76 (m, 1H), 1.49 (s, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.20 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (75 MHz) δ 214.6 (C), 136.5 (CH), 129.5 (CH), 109.0 (C), 83.5 (CH), 77.1 (CH), 59.8 (CH), 49.7 (C), 49.5 (CH), 38.6 (CH_2), 37.4 (C), 29.9 (CH_3), 28.5(CH_2), 25.4 (CH_3), 25.0 (two signals overlapping, 2 x CH_3).

IR ν_{max} 2965, 2937, 2910, 2883, 1734, 1381, 1367, 1265, 1206, 1088, 1066, 879, 738 cm^{-1}.

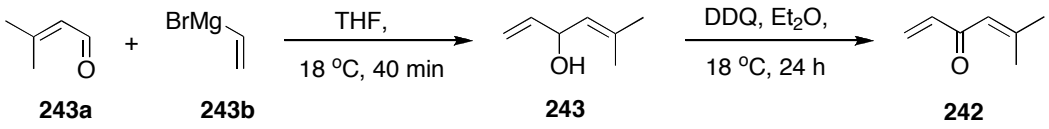
Mass spectrum (EI, 70 eV) *m/z* 262 ($M^{+\bullet}$, <1%), 247 [$(M - CH_3\bullet)^+$, 25], 204 (100), 175 (49), 161 (30), 147 (46), 119 (49), 91 (46), 65 (13), 55 (41), 43 (54).

HREIMS Found: $(M - CH_3\bullet)^+$, 247.1339. $C_{16}H_{22}O_3$ requires $(M - CH_3\bullet)^+$, 247.1334.

Optical Rotation $[\alpha]_D$ = -107 (*c* 0.95, $CHCl_3$).

5-Methylhexa-1,4-dien-3-one (242)

Method 1:



243a **243b** **243** **242**

Following a procedure established by Szymoniak *et al.*,[196] a solution of 3-methyl-but-2-enal (**243a**) (770 μL, 7.98 mmol) in THF (2 mL) was added dropwise to a solution of vinyl magnesium bromide (**243b**) (10 mL of a 1.0 M solution in THF, 10.0 mmol) in THF (5 mL) at 18 ºC. The ensuing mixture was stirred at this temperature for 40 min then water (5 mL) was added and the separated aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give allylic alcohol **243** (800 mg, *ca.* 89%) as an orange oil. This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 5.88 (ddd, *J* = 17.1, 10.3 and 5.8 Hz, 1H), 5.22 (dt, *J* = 17.1 and 1.5 Hz, 1H), 5.18 (dt, *J* = 10.3 and 1.5 Hz, 1H), 5.07 (dt, *J* = 7.1 and 1.2 Hz, 1H), 4.84 (uneven t, *J* = 7.1 and 5.8 Hz, 1H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.70 (d, *J* = 1.0 Hz, 3H) 1.67 (br s, 1H).

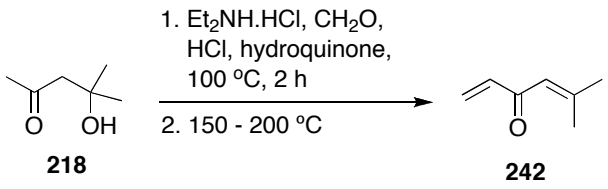
The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[123]

DDQ (555 mg, 2.44 mmol) was added to a solution of alcohol **243** (252 mg, 2.25 mmol) in Et_2O (1 mL) and the resulting slurry was stirred at 18 ºC for 24 h. The ensuing mixture was poured into pentane (10 mL) (to precipitate the $DDQH_2$), the flask washed with additional pentane (2 x 5 mL) and the resultant solid filtered off and washed with pentane (2 x 5 mL). The combined filtrates were carefully concentrated under reduced pressure (temp. = 40 ºC, pressure <750) to give (volatile) divinyl ketone **242** (101 mg, 41%) as a yellow liquid. This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 6.39 (dd, *J* = 17.5 and 10.4 Hz, 1H), 6.27 (qu, *J* = 1.3 Hz, 1H), 6.19 (dd, *J* = 17.5 and 1.5 Hz, 1H), 5.73 (dd, *J* = 10.4 and 1.5 Hz, 1H), 2.17 (d, *J* = 1.3 Hz, 3H), 1.93 (d, *J* = 1.3 Hz, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[139]

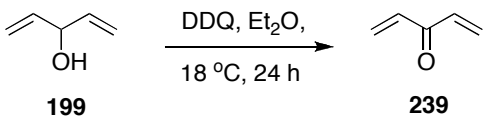
Method 2:



218 **242**

Following a procedure established by Mironov *et al.*,[138] diethylamine hydrochloride (6.85 g, 62.5 mmol), formaldehyde (5.1 mL of a 37% aqueous solution, 62.5 mmol), 4-hydroxy-4-methylpentan-2-one (**218**) (7.75 mL, 62.5 mmol), HCl (250 μL of a 36% aqueous solution) and hydroquinone (125 mg, 1.14 mmol) were combined in a pyrex sealed reaction vessel and the contents was heated at 100 °C for 2 h. After cooling, the sealed tube was carefully opened and the reaction mixture transferred to a distillation apparatus (as the scale of the reaction was constrained by the size of the sealed tubes several batch runs were carried out simultaneously and combined at this point). After distilling off the water, the hydrochloride salt of the Mannich base was decomposed at 150–210 °C to give the title divinyl ketone **242** (2.4 g, 35%), which was obtained as a bright yellow liquid contaminated with mesityl oxide, ρ_{20} = 0.880 mg/mL. This material was used directly in the next step of the reaction sequence.

1,4-Pentadien-3-one (239)



199 **239**

DDQ (12.8 g, 56.6 mmol) was added to a solution of 1,4-pentadien-3-ol (**199**) (5.0 mL, 51.4 mmol) in Et_2O (20 mL, 2.5 M) and the resulting slurry was stirred at 18 ºC for 24 h. The ensuing mixture was then poured into pentane (100 mL) (to precipitate the $DDQH_2$), the flask washed with additional pentane (2 x 20 mL) and the resultant solid filtered off and washed with pentane (2 x 20 mL). The combined filtrates were carefully concentrated under reduced pressure (temp. = 40 ºC, pressure <750) to give divinyl ketone **239** as a 60% solution in Et_2O/pentane (*ca.* 6 mL, 72%). This material was used directly in the next step of the reaction sequence. For the purposes of characterization, a small sample of the solution was concentrated to afford title divinyl ketone **239** as a clear, bright-yellow liquid.

^{1}H NMR (300 MHz) δ 6.64 (dd, *J* = 17.4 and 10.6 Hz, 2H), 6.32 (dd, *J* = 17.4 and 1.3 Hz, 2H), 5.88 (dd, *J* = 10.6 and 1.3 Hz, 2H).

The data presented above matched the equivalent spectral information reported in the literature.[141] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

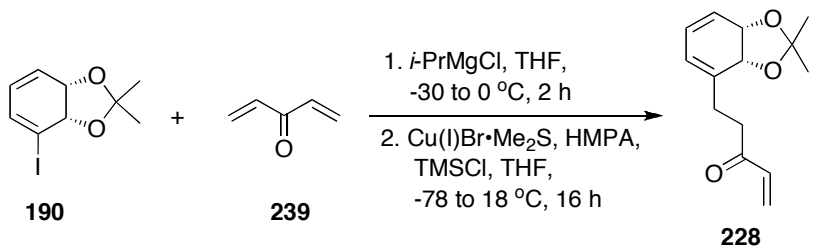
^{13}C NMR (75 MHz) δ 190.1 (C), 134.2 (CH), 129.4 (CH_2).
IR ν_{max} 2926, 2857, 1698, 1679, 1613, 1403, 1090, 989, 928 cm^{-1}.

General Procedure for the Michael addition of protected 3-iodocyclohexa-3,5-diene-1,2-diols to enones

A solution of iodo-diol (1.0 mole equiv.) in THF (0.2 M) was cooled to -30 °C then treated dropwise with *i*-PrMgCl (1.2–2.0 mole equiv. of a 2.0 M solution in THF). The ensuing mixture was warmed to 0 °C and stirred at this temperature until no starting material could be seen by ^{1}H NMR analysis (1–2 h). The reaction mixture was then cooled to -78 °C and treated with copper (I) bromide-dimethyl sulfide complex (0.1 mole equiv.) and HMPA (3.0 mole equiv.). A solution of enone (2.1 mole equiv.) and TMSCl (3.0 mole equiv.) in THF (*ca*. 2 mL) was then added dropwise, *via* syringe pump, over 1.5 h. The resulting mixture was allowed to warm to 18 ºC over 16 h then treated with NH_4Cl (*ca*. 20 mL of a saturated aqueous solution) and stirred at

18 ºC for 10 min. The biphasic system was separated and the aqueous layer was extracted with EtOAc (3 x *ca*. 30 ml). The combined organic fractions were washed with water (2 x *ca*. 10 mL) and brine (*ca*. 20 mL) then dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude material thus obtained was subjected to flash column chromatography using the conditions defined below for each individual case.

5-[(3a*R*,7a*S*)-2,2-Dimethyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]pent-1-en-3-one (228)

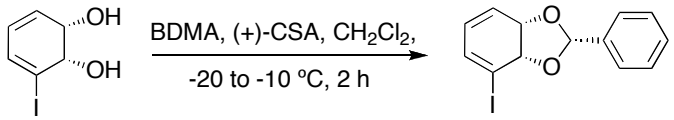


190 **239** **228**

The Michael addition of iodo-diol **190** (503 mg, 1.81 mmol) to enone **239** (591 μL of a 60% solution in Et_2O/pentane, *ca*. 3.80 mmol) was carried out as described in the general procedure and using 1.2 mole equiv. of *i*-PrMgCl (1.1 mL of a 2.0 M solution in THF, 2.2 mmol). The crude product thus obtained was subjected to flash column chromatography (1:9 *v/v* EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4, 3:7 *v/v* EtOAc/hexane) gave the *title enone **228*** (274 mg, 65%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.37 (dd, *J* = 17.7 and 10.3 Hz, 1H), 6.23 (dd, *J* = 17.7 and 1.5 Hz, 1H), 5.96 (dd, *J* = 9.6 and 5.6 Hz, 1H), 5.84 (dd, *J* = 10.3 and 1.5 Hz, 1H), 5.79 (dd, *J* = 9.6 and 3.8 Hz, 1H), 5.71 (d, *J* = 5.6 Hz, 1H), 4.66 (dd, *J* = 8.7 and 3.8 Hz, 1H), 4.53 (d, *J* = 8.7 Hz, 1H), 2.83 (td, *J* = 7.5 and 3.0 Hz, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 1.39 (s, 3H), 1.38 (s, 3H).
^{13}C NMR (75 MHz) δ 199.8 (C), 136.9 (C), 136.4 (CH), 128.2 (CH_2), 124.4 (CH), 123.1 (CH), 118.9 (CH), 105.3 (C), 73.4 (CH), 71.2 (CH), 37.4 (CH_2), 27.9 (CH_2), 26.8 (CH_3), 25.0 (CH_3).
IR ν_{max} 3044, 2985, 2933, 2894, 1700, 1681, 1402, 1378, 1369, 1208, 1158, 1096, 1031, 962, 838, 717 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 234 ($M^{+\bullet}$, <1%), 176 (48), 158 (75), 147 (40), 121 (75), 107 (100), 91 (46), 77 (52), 55 (95), 43 (62).
HREIMS Found: $M^{+\bullet}$, 234.1255. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256.
Optical Rotation $[\alpha]_D$ = +89 (*c* 1.6, $CHCl_3$).

(2*S*,3a*S*,7a*S*)-4-Iodo-2-phenyl-3a,7a-dihydro-1,3-benzodioxole (245)



88 **245**

A suspension of (1*S*,2*S*)-3-iodocyclohexa-3,5-diene-1,2-diol (**88**) (1.00 g, 4.20 mmol) and (1*S*)-(+)-10-camphorsulfonic acid monohydrate (20.0 mg, 0.08 mmol) in CH_2Cl_2 (30 mL) was cooled to -20 ºC then benzaldehyde dimethylacetal (650 μL, 4.33 mmol) was added in a dropwise manner. The ensuing mixture was allowed to warm to -10 ºC over 2 h then NaOH (20 mL of a 2.0 M aqueous solution) was added. The separated aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic fractions were washed with water (20 mL) and brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the *title acetal* ***245*** (containing traces of benzaldehyde) (1.29 g, *ca.* 85%) as an unstable white solid (R_f = 0.6, 3:7 *v/v* EtOAc/hexane). This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 7.50 (m, 2H), 7.37 (m, 3H), 6.70 (dt, *J* = 6.0 and 0.7 Hz, 1H), 6.09 (ddt, *J* = 9.5, 4.1 and 0.7 Hz, 1H), 5.81 (dd, *J* = 9.5 and 6.0 Hz, 1H), 5.77 (s, 1H), 4.83 (d, *J* = 9.2 Hz, 1H), 4.70 (dd, *J* = 9.2 and 4.1 Hz, 1H).

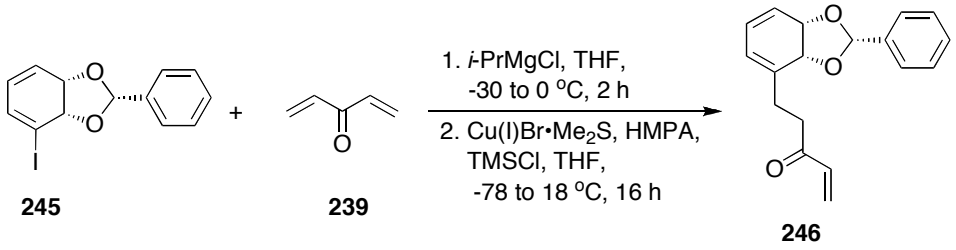
^{13}C NMR (75 MHz) δ 136.0 (C), 133.7 (CH), 129.6 (CH), 128.3 (CH), 127.2 (CH), 125.2 (CH), 123.7 (CH), 99.1 (CH), 98.5 (C), 77.9 (CH), 72.8 (CH).

IR ν_{max} 2880, 1458, 1395, 1364, 1333, 1312, 1284, 1216, 1087, 1059, 1009, 987, 948, 927, 838, 762, 701 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 326 ($M^{+\bullet}$, 21%), 280 (76), 204 (65), 171 (50), 153 (82), 105 (92), 93 (90), 77 (99), 65 (100), 51 (69), 39 (75).

HREIMS Found: $M^{+\bullet}$, 325.9804. $C_{13}H_{11}O_2{}^{127}I$ requires $M^{+\bullet}$, 325.9804.

5-[(2*S*,3a*R*,7a*S*)-2-Phenyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]pent-1-en-3-one (246)

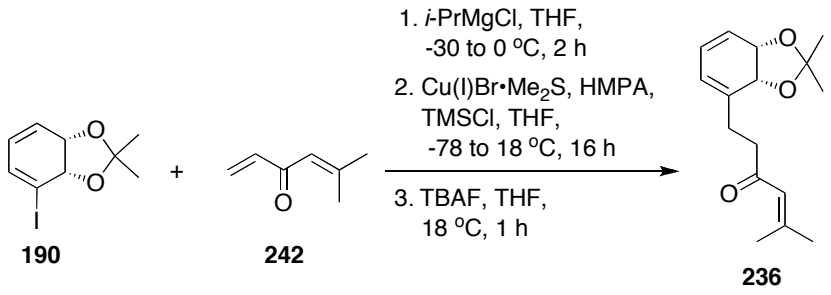


245 **239** **246**

The Michael addition of iodo-diol **245** (690 mg, *ca.* 2.12 mmol) to enone **239** (691 μL of a 60% solution in Et_2O/pentane, *ca.* 4.44 mmol) was carried out as described in the general procedure using 2.0 mole equiv. of *i*-PrMgCl (2.1 mL of a 2.0 M solution in THF, 4.2 mmol). The crude product was subjected to flash column chromatography (1:9 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) gave the *title enone* ***246*** (376 mg, 63%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.45 (m, 2H), 7.35 (m, 3H), 6.34 (dd, *J* = 17.8 and 10.4 Hz, 1H), 6.19 (dd, *J* = 17.8 and 1.3 Hz, 1H), 6.02 (dd, *J* = 9.5 and 5.6 Hz, 1H), 5.89 (dd, *J* = 9.5 and 3.7 Hz, 1H), 5.80 (dd, *J* = 10.4 and 1.3 Hz, 1H), 5.80 (d, partially obscured, *J* = 5.6, 1H), 5.70 (s, 1H), 4.73 (dd, *J* = 9.3 and 3.7 Hz, 1H), 4.60 (d, *J* = 9.3 Hz, 1H), 2.84 (m, 2H), 2.62 (m, 2H).
^{13}C NMR (75 MHz) δ 199.8 (C), 136.8 (C), 136.3 (CH), 135.9 (C), 129.4 (CH), 128.3 (CH), 128.2 (CH_2), 127.0 (CH), 124.5 (CH), 122.2 (CH), 119.4 (CH), 99.1 (CH), 74.1 (CH), 72.3 (CH), 37.5 (CH_2), 28.1 (CH_2).
IR ν_{max} 3045, 2891, 1711, 1459, 1402, 1374, 1312, 1294, 1218, 1089, 1065, 1025, 1000, 919, 761, 735, 699 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 282 ($M^{+\bullet}$, <1%), 175 (62), 158 (91), 147 (55), 133 (35), 121 (72), 105 (90), 91 (52), 77 (85), 65 (28), 55 (100), 39 (31).
HREIMS Found: $M^{+\bullet}$, 282.1254. $C_{18}H_{18}O_3$ requires $M^{+\bullet}$, 282.1256.
Optical Rotation $[\alpha]_D$ = +112 (*c* 1.5, $CHCl_3$).

1-[(3a*R*,7a*S*)-2,2-Dimethyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]-5-methylhex-4-en-3-one (236)



The Michael addition of iodo-diol **190** (1.00 g, 3.60 mmol) to enone **242** (945 μL, *ca.* 7.55 mmol) was carried out as described in the general procedure using 1.5 mole equiv. of *i*-PrMgCl (2.7 mL of a 2.0 M solution in THF, 5.4 mmol). The initially formed product was a silyl enol ether so this was dissolved in THF (7 mL) then treated with tetra-*n*-butylammonium fluoride (7 mL of a 1.0 M solution in THF, 7.00 mmol) and stirred at 18 ºC for 1 h. The ensuing mixture was concentrated under reduced pressure onto silica (*ca.* 2 g, 230–400 mesh) and the resulting free-flowing solid subjected to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4, 3:7 *v/v* EtOAc/hexane) gave the *title enone **236*** (700 mg, 74%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.09 (qu, *J* = 1.2 Hz, 1H), 5.96 (dd, *J* = 9.7 and 5.6 Hz, 1H), 5.78 (dd, *J* = 9.7 and 3.7 Hz, 1H), 5.70 (d, *J* = 5.6 Hz, 1H), 4.66 (dd, *J* = 8.6 and 3.7 Hz, 1H), 4.53 (d, *J* = 8.6 Hz, 1H), 2.65 (m, 2H), 2.53 (m, 2H), 2.34 (d, *J* = 1.1 Hz, 3H), 1.89 (d, *J* = 1.1 Hz, 3H), 1.40 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (75 MHz) δ 199.9 (C) 155.4 (C), 137.3 (C), 124.5 (CH), 123.6 (CH), 122.9 (CH), 118.6 (CH), 105.3 (C), 73.5 (CH), 71.3 (CH), 41.8 (CH_2), 28.1 (CH_2), 27.7 (CH_3), 26.9 (CH_3), 25.0 (CH_3), 20.8 (CH_3).

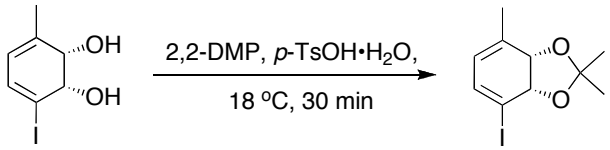
IR ν_{max} 3044, 2948, 2933, 2912, 1688, 1620, 1445, 1378, 1369, 1234, 1209, 1159, 1109, 1031, 961, 888, 708 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 262 ($M^{+\bullet}$, 2%), 247 (2), 204 (33), 189 (10), 149 (34), 121 (33), 104 (50), 91 (23), 83 (100), 77 (29), 65 (12), 55 (69), 43 (35), 39 (21).

HREIMS Found: $(M - CH_3\bullet)^+$, 247.1334. $C_{16}H_{22}O_3$ requires $(M - CH_3\bullet)^+$, 247.1334.

Optical Rotation $[\alpha]_D$ = +114 (*c* 0.3, $CHCl_3$).

(3a*S*,7a*S*)-3a,7a-Dihydro-4-iodo-2,2,7-trimethylbenzo[*d*][1,3]dioxole (247)



247a **247**

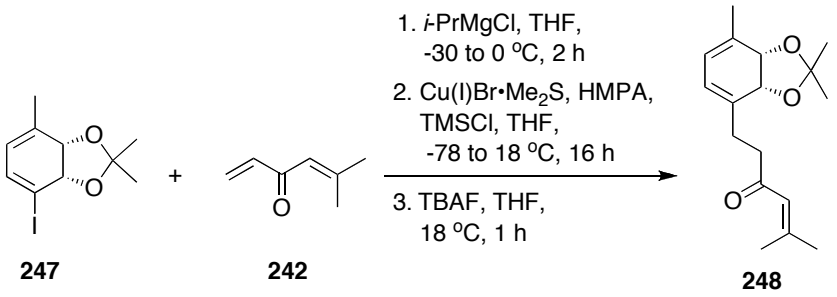
A solution of (1*S*,2*S*)-3-iodo-6-methylcyclohexa-3,5-diene-1,2-diol (**247a**) (2.0 g, 7.93 mmol) in 2,2-dimethoxypropane (40 mL) was treated with *p*-TsOH•H_2O (*ca*. 30 mg, 0.16 mmol) at 18 ºC and stirred at this temperature for 30 min then quenched with triethylamine (1.0 mL) and concentrated under reduced pressure. The resulting brown residue was partitioned between water (40 mL) and Et_2O (100 mL) and the separated aqueous phase was extracted with Et_2O (2 x 200 mL). The combined organic phases were washed with NaOH (100 mL of a 2.0 M solution) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure (temp. = 30 ºC) to give title acetonide **247** (2.17 mg, 93%) as a pale-brown oil (R_f = 0.6, 3:7 *v/v* EtOAc/hexane). This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 6.54 (d, *J* = 6.2 Hz, 1H), 5.49 (dq, *J* = 6.2 and 1.6 Hz, 1H), 4.73 (d, *J* = 8.4 Hz, 1H), 4.46 (dd, *J* = 8.4 and 0.7 Hz, 1H), 1.88 (d, *J* = 0.7 Hz, 3H), 1.43 (s, 3H), 1.42 (s, 3H).

Optical Rotation $[\alpha]_D$ = +37 (*c* 1.0, $CHCl_3$) [lit.[197] $[\alpha]_D$ = +69 (*c* 0.77, $CHCl_3$)].

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[197]

5-Methyl-1-[(3a*R*,7a*S*)-2,2,7-trimethyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]hex-4-en-3-one (248)



The Michael addition of iodo-diol **247** (1.00 g, 3.42 mmol) to enone **242** (900 μL, *ca.* 7.20 mmol) was carried out as described in the general procedure using 2.0 mole equiv. of *i*-PrMgCl (3.4 mL of a 2.0 M solution in THF, 6.8 mmol). The initially formed product was a silyl enol ether so this was dissolved in THF (7 mL) then treated with tetra-*n*-butylammonium fluoride (7 mL of a 1.0 M solution in THF, 7.00 mmol) and stirred at 18 ºC for 1 h. The ensuing mixture was concentrated under reduced pressure onto silica (*ca.* 2 g, 230–400 mesh) and the resulting free-flowing solid subjected to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4, 3:7 *v/v* EtOAc/hexane) gave the *title enone **248*** (568 mg, 60%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.09 (m, 1H), 5.65 (s, 2H), 4.50 (AB quartet, *J* = 8.4 Hz, 2H), 2.63 (m, 2H), 2.51 (m, 2H), 2.13 (s, 3H), 1.88 (s, 3H), 1.86 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (75 MHz) δ 200.0 (C), 155.1 (C), 134.1 (C), 132.3 (C), 123.6 (CH), 119.7 (CH), 119.6 (CH), 105.8 (C), 75.6 (CH), 74.3 (CH), 42.1 (CH_2), 28.3 (CH_2), 27.6 (CH_3), 27.0 (CH_3), 25.3 (CH_3), 20.7 (CH_3), 19.8 (CH_3).

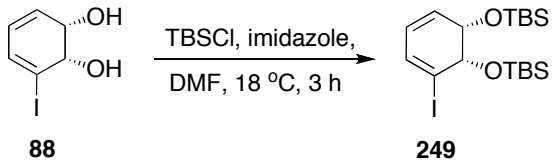
IR ν_{max} 2982, 2933, 2912, 1688, 1620, 1447, 1278, 1269, 1235, 1208, 1180, 1158, 1110, 1062, 1039, 1013, 872 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 261 [$(M - CH_3\cdot)^+$, <1%], 218 (49), 199 (19), 191 (22), 185 (18), 163 (39), 149 (58), 135 (55), 121 (90), 108 (26), 91 (39), 83 (100), 77 (35), 55 (81), 43 (82).

HREIMS Found: $M^{+\bullet}$, 276.1722. $C_{17}H_{24}O_3$ requires $M^{+\bullet}$, 276.1725. Found: $(M - CH_3\cdot)^+$, 261.1491. $C_{17}H_{24}O_3$ requires $(M - CH_3\cdot)^+$, 261.1491.

Optical Rotation $[\alpha]_D$ = +19 (*c* 0.9, $CHCl_3$).

[[(1*S*,2*S*)-3-Iodocyclohexa-3,5-diene-1,2-diyl]bis(oxy)]bis[*tert*-butyl(dimethyl)silane] (249)

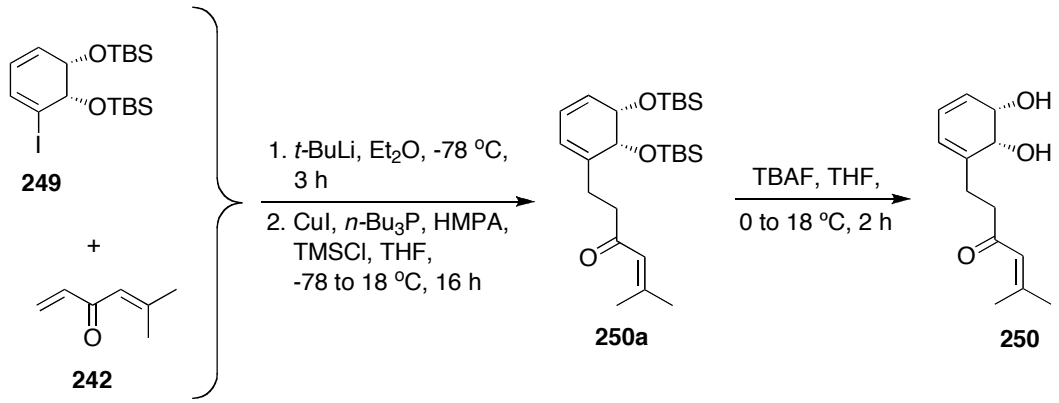


88 **249**

A solution of *t*-butyldimethylsilyl chloride (2.45 g, 16.3 mmol) in dry DMF (5.3 mL) was added dropwise to a solution of diol **88** (1.0 g, 4.20 mmol) and imidazole (1.73 g, 25.4 mmol) in dry DMF (12.8 mmol) at 18 ºC. After stirring for 3 h at this temperature the reaction mixture was diluted with water (100 mL) and Et_2O (150 mL). The separated aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic phases were washed with water (2 x 20 mL) and brine (20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give *compound **249*** (1.76 g, 90%) as an unstable brown oil, (R_f = 0.6, 1:9 *v/v* EtOAc/hexane). This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 6.62 (d, *J* = 5.5 Hz, 1H), 5.89 (dd, *J* = 9.5 and 2.7 Hz, 1H), 5.65 (dd, *J* = 9.5, 5.5 and 2.2 Hz, 1H), 4.43 (m, 1H), 4.08 (d, *J* = 4.9 Hz, 1H), 0.92 (s, 9H), 0.91 (s, 9H), 0.17–0.10 (m, 12H).

1-[(5*S*,6*R*)-5,6-Dihydroxycyclohexa-1,3-dien-1-yl]-5-methylhex-4-en-3-one (250)



A solution of iodide **249** (127 mg, 0.27 mmol) in Et_2O (2 mL) was cooled to -78 °C then treated, dropwise, with *t*-BuLi (320 μL of a 1.7 M solution in pentane, 0.54 mmol). The ensuing mixture was stirred at -78 °C for 3 h. In a separate flask, a slurry of anhydrous copper (I) iodide (52.0 mg, 0.27 mmol) in THF (2 mL) was treated with tri-*n*-butyl phosphine (170 μL, 0.68 mmol) and the mixture was stirred until it became a colourless solution. This mixture was cooled to -78 °C then added, *via* cannula, to the organolithium derivative. The resulting orange

solution was stirred at -78 °C for 15 min then treated with HMPA (143 μL, 0.82 mmol). A solution of divinyl ketone **242** (73 μL, 0.58 mmol) and TMSCl (104 μL, 0.82 mmol) in THF (5 mL) was then added dropwise over 3 h. After the addition was complete the reaction mixture was warmed to 18 ºC and allowed to stir at this temperature for 13 h. The reaction mixture was then poured into NH_4Cl (10 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with Et_2O (3 x 30 mL). Combined organic phases were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give compound **250a** as a yellow oil. This material was dissolved in THF (2 mL) and the resultant solution was cooled to 0 ºC. tetra-*n*-Butylammonium fluoride (1.36 mL of a 1.0 M solution in THF, 1.37 mmol) was then added and the ensuing mixture was allowed to warm to 18 ºC and stirred at this temperature for 2 h. $NaHCO_3$ (10 mL of a 50% *w/v* aqueous solution) were then added and the separated aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the ensuing residue by flash column chromatography (silica, 1:1 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) gave the *title diol* ***250*** (19.9 mg, 33%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.09 (s, 1H), 5.91 (ddd, *J* = 9.6, 5.4 and 1.0 Hz, 1H), 5.80 (dd, *J* = 9.6 and 3.4 Hz, 1H), 5.68 (d, *J* = 5.4 Hz, 1H), 4.27 (br s, 1H), 4.07 (br t, *J* = 6.1 Hz, 1H), 2.93 (br d, *J* = 7.1 Hz, 1H), 2.67 (t, *J* = 7.1 Hz, 2H), 5.52 (t, *J* = 7.1 Hz, 2H), 2.45 (br d, *J* = 7.6 Hz, 1H), 2.13 (s, 3H), 1.89 (s, 3H).

^{13}C NMR (75 MHz) δ 200.5 (C), 156.4 (C), 140.9 (C), 127.8 (CH), 124.7 (CH), 123.5 (CH), 119.9 (CH), 70.3 (CH), 68.7 (CH), 42.7 (CH_2), 27.7(4) (CH_2), 27.7(3) (CH_3), 20.9 (CH_3)

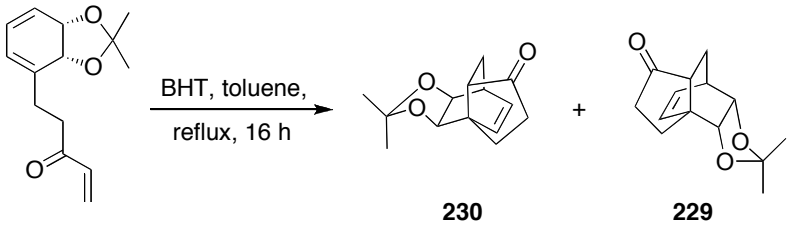
IR ν_{max} 3372, 2921, 2853, 1684, 1618, 1444, 1380, 1231, 1142, 1109, 1075, 1032, 923, 809, 681 cm^{-1}

Mass spectrum (EI, 70 eV) *m/z* 222 ($M^{+\bullet}$, <1%), [$(M - H_2O)^{+\bullet}$, 26], 148 (18), 121 (24), 107 (41), 91 (17), 83 (100), 77 (27), 55 (54), 39 (25)

HREIMS Found: $M^{+\bullet}$, 222.1256. $C_{13}H_{18}O_3$ requires $M^{+\bullet}$, 222.1256

Optical Rotation $[\alpha]_D$ = +5.8 (*c* 0.5, $CHCl_3$)

(3a*S*,4*S*,5a*S*,8a*S*,8b*R*)-2,2-Dimethylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (230) and (3a*S*,4*R*,5a*R*,8a*R*,8b*R*)-2,2-dimethylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (229)



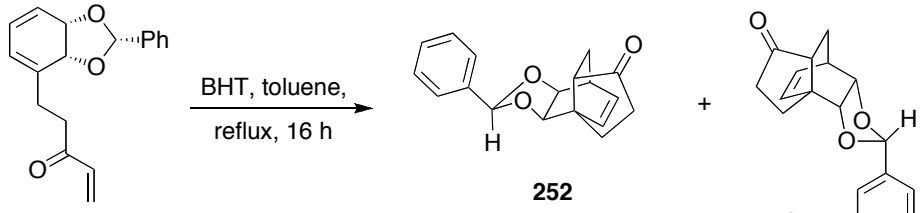
228 **230** **229**

A solution of enone **228** (258 mg, 1.10 mmol) and BHT (24.7 mg, 0.11 mmol) in toluene (110 mL) was heated at reflux for 16 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue thus obtained was subjected to flash column chromatography (silica, 1:4 → 2:3 *v/v* EtOAc/hexane gradient elution) and so affording two fractions, A and B.

Concentration of fraction A (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) gave the title *syn*-adduct **230** (101 mg, 39%) as a white crystalline solid, which was identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.2, 3:7 *v/v* EtOAc/hexane) gave the title *anti*-adduct **229** (113 mg, 44%) as a white crystalline solid, which was identical, in all respects, with authentic material.

(2*S*,3a*S*,4*S*,5a*S*,8a*S*,8b*R*)-2-Phenylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (252) and (2*S*,3a*S*,4*R*,5a*R*,8a*R*,8b*R*)-2-phenylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (251)



246 **252** **251**

A solution of enone **246** (129 mg, 0.46 mmol) and BHT (10 mg, 0.05 mmol) in toluene (45 mL) was heated at reflux for 24 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue thus obtained was subjected to flash column chromatography (silica, 1:9 → 3:7 *v/v* EtOAc/hexane gradient elution) and so affording two fractions, A and B.

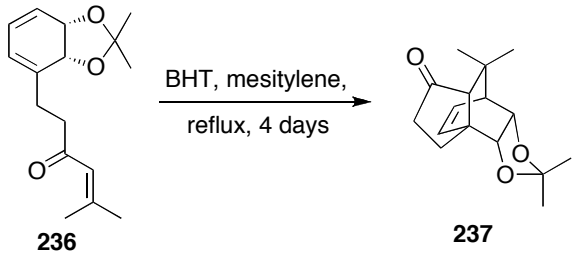
Concentration of fraction A (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded the *title syn-adduct* ***252*** (27 mg, 21%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.50 (m, 2H), 7.41 (m, 3H), 6.41 (dd, *J* = 8.1 and 6.8 Hz, 1H), 5.94 (s, 1H), 5.89 (d, *J* = 8.1 Hz, 1H), 4.14 (dd, *J* = 8.4 and 3.9 Hz, 1H), 4.07 (d, *J* = 8.4 Hz, 1H), 3.02 (m, 1H), 2.84 (ddd, *J* = 9.8, 6.1 and 1.5 Hz, 1H), 2.49–1.99 (complex m, 5H), 1.50 (ddd, *J* = 12.7, 6.8 and 1.5 Hz, 1H).
^{13}C NMR (75 MHz) δ 217.4 (C), 137.3 (CH), 136.4 (C), 134.1 (CH), 129.8 (CH), 128.6 (CH), 126.8 (CH), 106.2 (CH), 77.8 (CH), 76.3 (CH), 47.8 (C), 46.1 (CH), 36.2 (CH_2), 35.0 (CH), 25.2 (CH_2), 23.2 (CH_2) .
IR ν_{max} 3041, 2917, 2869, 1740, 1458, 1405, 1298, 1220, 1444, 1108, 1086, 1063, 1025, 991, 884, 761, 743, 700, 643 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 282 ($M^{+\bullet}$, 5%), 253 (51), 176 (71), 159 (15), 147 (82), 133 (82), 120 (40), 105 (96), 91 (100), 77 (61), 65 (21), 55 (32), 51 (20), 41 (24).
HREIMS Found: $M^{+\bullet}$, 282.1255. $C_{18}H_{18}O_3$ requires $M^{+\bullet}$, 282.1256.
Optical Rotation $[\alpha]_D$ = +59 (*c* 0.3, $CHCl_3$).

Concentration of fraction B (R_f = 0.1, 3:7 *v/v* EtOAc/hexane) afforded the *title anti-adduct* ***251*** (76 mg, 59%) as a white crystalline solid, m.p. = 174–179 ºC.

^{1}H NMR (300 MHz) δ 7.47 (m, 2H), 7.35 (m, 3H), 6.44 (br t, *J* = 7.3 Hz, 1H), 5.89 (d, *J* = 8.3 Hz, 1H), 5.63 (s, 1H), 4.34 (dd, *J* = 7.4 and 2.7 Hz, 1H), 4.28 (d, *J* = 7.4 Hz, 1H), 3.08 (m, 1H), 2.49 (m, 2H), 2.29 (m, 1H), 2.01 (m, 2H), 1.65 (m, 2H).
^{13}C NMR (75 MHz) δ 214.9 (C), 136.2 (CH), 136.1 (C), 131.1 (CH), 129.8 (CH), 128.3 (CH), 127.5 (CH), 103.5 (CH), 83.8 (CH), 80.1 (CH), 50.3 (CH), 47.6 (C), 36.9 (CH_2), 35.6 (CH), 28.4 (CH_2), 23.7 (CH_2).
IR ν_{max} 2922, 2873, 1732, 1462, 1404, 1358, 1313, 1218, 1150, 1112, 1084, 1062, 1028, 1019, 1010, 994, 920, 853, 759, 698, 642 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 281 [$(M - H\bullet)^+$, 12%], 253 (9), 176 (69), 158 (18), 147 (68), 133 (58), 120 (40), 105 (100), 91 (67), 77 (45), 65 (18), 55 (21), 51 (15), 39 (16).
HREIMS Found: $(M - H\bullet)^+$, 281.1176. $C_{18}H_{18}O_3$ requires $(M - H\bullet)^+$, 281.1178.
Optical Rotation $[\alpha]_D$ = -75 (*c* 0.5, $CHCl_3$).

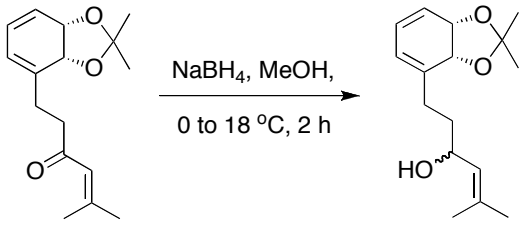
(3a*S*,4*S*,5a*R*,8a*R*,8b*R*)-2,2,5,5-Tetramethylhexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (237)



236 **237**

A solution of enone **236** (129 mg, 0.46 mmol) and BHT (10 mg, 0.05 mmol) in mesitylene (45 mL) was heated at reflux for 4 days. The cooled reaction mixture was then concentrated under reduced pressure and subjected to flash column chromatography (silica, 1:9 → 3:7 *v/v* EtOAc/hexane gradient elution) to afford compound **237** (58.1 mg, 45%) as a white crystalline solid. This material was identical, in all respects, with authentic material.

1-[(3a*R*,7a*S*)-2,2-Dimethyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]-5-methylhex-4-en-3-ol (253)



236 **253**

A solution of enone **236** (100 mg, 0.40 mmol) in MeOH (4 mL) was cooled to 0 ºC and treated with $NaBH_4$ (29 mg, 0.77 mmol). The ensuing mixture was stirred at 0 ºC for 1 h then warmed to 18 ºC and stirred at this temperature for a further 1 h. Water (1 mL) was added then the solvents were removed under reduced pressure. The residue thus obtained was partitioned between half brine (10 mL) and CH_2Cl_2 (20 mL) then the separated aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic fractions were washed with brine (10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 → 3:7 *v/v* EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.4, 1:1 *v/v* EtOAc/hexane) gave a *ca.* 1:1 mixture of the epimeric forms of *alcohol **253*** (88 mg, 84%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.96 (ddd, *J* = 9.6, 5.6 and 1.6 Hz 1H), 5.76 (m, 2H), 5.19 (m, 1H), 4.66 (dd, *J* = 8.6 and 3.7 Hz, 1H), 5.12 (dd, *J* = 8.6 and 2.6 Hz, 1H), 4.37 (m, 1H), 2.26 (m, 2H), 1.83–1.55 (m, 2H), 1.72 (s, 3H), 1.68 (s, 1.5H), 1.66 (1.5H), 1.40 (s, 3H), 1.38 (s, 1.5H), 1.37 (s, 1.5H) (OH proton resonances not observed).

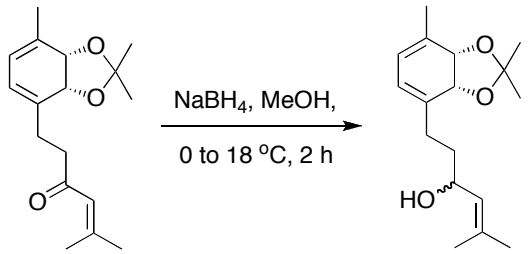
^{13}C NMR (75 MHz) δ 138.0 (C), 137.8 (C), 135.6 (C), 135.2 (C), 127.9 (CH), 127.8 (CH), 124.5 (two signals overlapping, 2 x CH), 122.8(4) (CH), 122.7(7) (CH), 118.6 (CH), 118.5 (CH), 105.2(4) (C), 105.1(8) (C), 73.4(9) (CH), 73.4(7) (CH), 71.4(4) (CH), 71.4(0) (CH), 68.4 (CH), 68.1 (CH), 35.2 (CH_2), 35.0 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.9 (CH_3), 26.8 (CH_3), 25.7(9) (CH_3), 25.7(7) (CH_3), 25.1 (CH_3), 25.0 (CH_3), 18.3(2) (CH_3), 18.2(5) (CH_3).

IR ν_{max} 3435, 3044, 2984, 2931, 1448, 1402, 1377, 1235, 1209, 1158, 1046, 886, 716 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 246 [$(M - H_2O)^{+\bullet}$, 1%), 231 [$(M - H_2O - CH_3\bullet)^+$, 4], 206 (60), 188 (42), 173 (51), 145 (35), 133 (41), 107 (100), 95 (52), 85 (54), 79 (59), 67 (31), 55 (36), 43 (71).

HREIMS Found: $(M - H_2O)^{+\bullet}$, 246.1614. $C_{16}H_{24}O_3$ requires $(M - H_2O)^{+\bullet}$, 246.1620.

5-Methyl-1-[(3a*R*,7a*S*)-2,2,7-trimethyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]hex-4-en-3-ol (254)



248 **254**

Alcohol **254** was prepared in the same manner described immediately above for congener **253** but now using enone **248** (107 mg, 0.39 mmol) as the starting material. In this manner a *ca.* 1:1 mixture of the epimeric forms of the *title alcohol **254*** (89 mg, 83%) was obtained as a clear colourless oil, (R_f = 0.2, 3:7 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 5.69 (m, 2H), 5.19 (m, 1H), 4.51 (s, 2H), 4.37 (m, 1H), 2.25 (m, 2H), 1.87 (s, 3H), 1.84–1.57 (m, 2H), 1.72 (s, 3H), 1.68 (s, 1.5H), 1.66 (s, 1.5H), 1.42 (s, 3H), 1.37 (s, 1.5H), 1.35 (s, 1.5H) (OH proton resonances not observed).

^{13}C NMR (75 MHz) δ 135.5 (C), 135.2 (C), 134.8 (C), 134.6 (C), 132.2 (C), 132.1 (C), 128.0 (CH), 127.9 (CH), 119.7 (CH), 119.6 (three signals overlapping, 3 x CH), 105.7(9) (C), 105.7(6) (C), 75.8 (CH), 75.7 (CH), 74.4 (CH), 74.3 (CH), 68.4 (CH), 68.1 (CH), 35.4 (CH_2), 35.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 27.0(3) (CH_3), 26.9(9) (CH_3), 25.8 (two signals

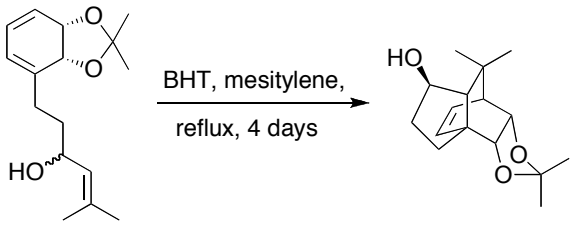
overlapping, 2 x CH_3), 25.4(3) (CH_3), 25.3(6) (CH_3), 19.8 (two signals overlapping, 2 x CH_3), 18.3(3) (CH_3), 18.2(6) (CH_3).

IR ν_{max} 3434, 2983, 2932, 2914, 2879, 1448, 1377, 1235, 1209, 1159, 1064, 1045, 1021, 872, 849 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 260 [$(M - H_2O)^{+\bullet}$, 6%), 245 [$(M - H_2O - CH_3\cdot)^{+}$, 10], 220 (92), 202 (52), 187 (67), 178 (25), 159 (40), 147 (48), 133 (27), 121 (100), 108 (59), 95 (69), 91 (53), 85 (68), 77(51), 67 (30), 55 (40), 43 (65).

HREIMS Found: $(M - H_2O)^{+\bullet}$, 260.1777. $C_{17}H_{26}O_3$ requires $(M - H_2O)^{+\bullet}$, 260.1776.

(3a*S*,4*S*,5a*R*,6*R*,8a*R*,8b*R*)-2,2,5,5-Tetramethyloctahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6-ol (255)



253 **255**

A solution of a *ca.* 1:1 mixture of the epimeric forms of alcohol **253** (43.3 mg, 0.16 mmol) and BHT (3.5 mg, 0.02 mmol) in mesitylene (35 mL) was heated at reflux for 4 days then cooled and concentrated under reduced pressure to give a yellow oil. Purification of this material by flash column chromatography (silica, 3:7 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 1:1 *v/v* EtOAc/hexane) afforded the *title compound **255*** (19.1 mg, 44%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.11 (dd, *J* = 8.1 and 6.5 Hz, 1H), 5.70 (dd, *J* = 8.1 and 1.0 Hz, 1H), 4.59 (ddd, *J* = 7.1, 3.0 and 1.0 Hz, 1H), 4.07 (dd, *J* = 7.1 and 1.0 Hz, 1H), 3.87 (tt, *J* = 8.5 and 5.6 Hz, 1H), 2.42 (ddd, *J* = 6.5, 3.0 and 1.0 Hz, 1H), 2.21 (m, 1H), 1.90 (m, 2H), 1.60 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.23 (d, *J* = 9.3 Hz, 1H), 1.14 (s, 3H), 1.00 (s, 3H) (OH proton resonance not observed).

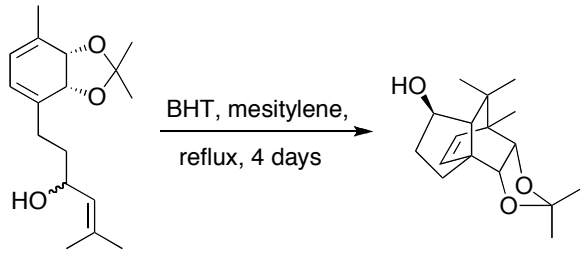
^{13}C NMR (75 MHz) δ 133.0 (CH), 132.3 (CH), 108.4 (C), 84.0 (CH), 77.2 (CH), 74.7 (CH), 59.8 (CH), 50.6 (C), 49.0 (CH), 35.1 (C), 34.0 (CH_2), 30.9 (CH_3), 30.1 (CH_2), 25.4(3) (CH_3), 25.3(6) (CH_3), 25.0 (CH_3).

IR ν_{max} 3435, 3042, 2931, 2869, 1456, 1378, 1368, 1264, 1206, 1174, 1161, 1091, 1064, 1029, 1006, 983, 967, 902, 884, 830, 816, 735, 702 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 264 ($M^{+\bullet}$, <1%), 249 (55), 206 (52), 188 (95), 173 (89), 164 (64), 159 (94), 145 (80), 133 (82), 120 (69), 105 (79), 100 (54), 91 (71), 85 (82), 77 (49), 69 (50), 55 (60), 43 (100).

HREIMS Found: $M^{+\bullet}$, 264.1726. $C_{16}H_{24}O_3$ requires $M^{+\bullet}$, 264.1725.

(3a*S*,4*S*,5a*R*,6*R*,8a*R*,8b*R*)-2,2,4,5,5-Pentamethyloctahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6-ol (256)



254 **256**

A solution of *ca.* 1:1 mixture of the epimeric forms of alcohol **254** (53.1 mg, 0.19 mmol) and BHT (4.0 mg, 0.02 mmol) in mesitylene (40 mL) was heated at reflux for 4 days then cooled and concentrated under reduced pressure to give a yellow oil. Purification of this material by flash column chromatography (silica, 3:7 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 1:1 *v/v* EtOAc/hexane) afforded the *title compound* ***256*** (24.3 mg, 46%) as a colourless, semi–solid.

^{1}H NMR (300 MHz) δ 5.68 (AB quartet, *J* = 8.3 Hz, 2H), 4.24 (d, *J* = 7.2 Hz, 1H), 4.08 (d, *J* = 7.2 Hz, 1H), 3.90 (m, 1H), 2.20 (m, 1H), 1.87 (m, 2H), 1.60 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.22 (d, *J* = 8.1 Hz, 1H), 1.19 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H) (OH proton resonance not observed).

^{13}C NMR (75 MHz) δ 137.9 (CH), 132.2 (CH), 108.3 (C), 84.9 (CH), 81.4 (CH), 74.8 (CH), 61.0 (CH), 49.4 (C), 46.3 (C), 37.4 (C), 34.0 (CH_2), 30.0 (CH_2), 27.0 (CH_3), 25.6 (CH_3), 25.0 (CH_3), 21.6 (CH_3), 15.0 (CH_3).

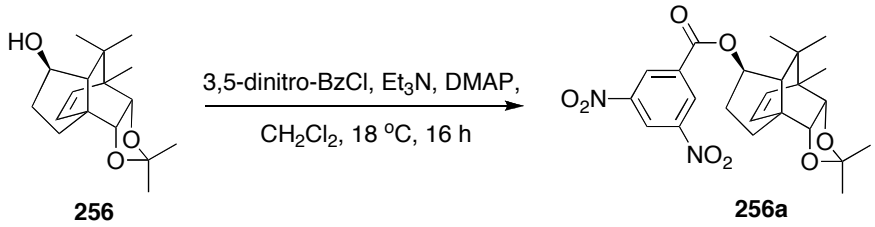
IR ν_{max} 3429, 3036, 2967, 2872, 1455, 1370, 1282, 1255, 1207, 1167, 1085, 1056, 1017, 898, 870, 733 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 263 [$(M - CH_3\cdot)^+$, 19%], 220 (73), 202 (28), 187 (31), 178 (99), 173 (39), 163 (48), 147 (41), 134 (41), 119 (100), 105 (42), 95 (38), 91 (41), 77 (27), 69 (18), 55 (35), 43 (64).

HREIMS Found: $(M - CH_3\cdot)^+$, 263.1647. $C_{17}H_{26}O_3$ requires $(M - CH_3\cdot)^+$, 263.1647.

Optical Rotation $[\alpha]_D$ = -5 (*c* 0.4, $CHCl_3$).

(3a*S*,4*S*,5a*R*,6*R*,8a*R*,8b*R*)-2,2,4,5,5-Pentamethyloctahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6-yl 3,5-dinitrobenzoate (256a)



256 **256a**

A solution of alcohol **256** (9.8 mg, 0.04 mmol), triethylamine (20 μL, 0.14 mmol) and 4-(*N,N*-dimethylamino)pyridine (17.3 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL) maintained at 18 ºC was treated with 3,5-dinitrobenzoyl chloride (24.2 mg, 0.105 mmol). The ensuing mixture was stirred at 18 ºC for 16 h then $NaHCO_3$ (2 mL of a saturated aqueous solution) and CH_2Cl_2 (5 mL) were added. The separated aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic fractions were washed with brine (2 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the resulting yellow oil by flash column chromatography (silica, 1:19 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.6, 3:7 *v/v* EtOAc/hexane) afforded *title ester* ***256a*** (10.1 mg, 61%) as a white crystalline solid, m.p. = 178–182 ºC

^{1}H NMR (300 MHz) δ 9.24 (t, *J* = 2.2 Hz, 1H), 9.12 (d, *J* = 2.2 Hz, 2H), 5.78 (AB quartet, *J* = 8.0 Hz, 2H), 5.09 (td, *J* = 9.0 and 5.6 Hz, 1H), 4.32 (d, *J* = 7.1 Hz, 1H), 4.19 (d, *J* = 7.1 Hz, 1H), 2.54 (m, 1H), 2.08 (ddd, *J* = 13.0, 9.0 and 3.2 Hz, 1H), 1.93 (td, *J* = 13.0 and 8.5 Hz, 1H), 1.80 (d, *J* = 9.0 Hz, 1H), 1.74 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H), 1.08 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (75 MHz) δ 162.1 (C), 148.7 (C), 138.8 (CH), 134.0 (C), 131.1 (CH), 129.3 (CH), 122.4 (CH), 108.7 (C), 84.5 (CH), 81.3 (CH), 80.2 (CH), 58.0 (CH), 49.2 (C), 46.3 (C), 37.6 (C), 31.1 (CH_2), 30.4 (CH_2), 26.9 (CH_3), 25.6 (CH_3), 25.0 (CH_3), 22.2 (CH_3), 15.1 (CH_3).

IR ν_{max} 3103, 2922, 2851, 1729, 1628, 1547, 1461, 1370, 1344, 1276, 1208, 1168, 1075, 1018, 920, 873, 804, 730, 721 cm^{-1}.

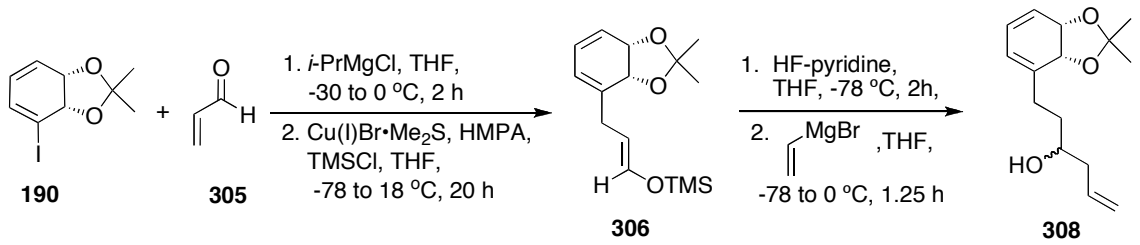
Mass spectrum (EI, 70 eV) *m/z* 457 [$(M - CH_3\cdot)^+$, 11%], 414 (22), 202 (100), 187 (39), 173 (50), 160 (58), 145 (79), 121 (45), 85 (30), 69 (40), 57 (51), 43 (77).

HREIMS Found: $(M - CH_3\cdot)^+$, 457.1609. $C_{24}H_{28}N_2O_8$ requires $(M - CH_3\cdot)^+$, 457.1611.

Optical Rotation $[\alpha]_D$ = -57 (*c* 0.15, $CHCl_3$).

5.4 Experimental Procedures for Chapter Four

1-[(3a*R*,7a*S*)-2,2-Dimethyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]hex-5-en-3-ol (308)



190 **305** **306** **308**

A solution of iodide **190** (910 mg, 3.27 mmol) in THF (16 mL, 0.2 M) was cooled to -30 °C then treated, dropwise, with *i*-PrMgCl (2.5 mL of a 2.0 M solution in THF, 5.0 mmol). The ensuing mixture was allowed to warm to 0 °C over 2 h after which time ^{1}H NMR analysis of the reaction mixture revealed that no starting material remained. Accordingly, the mixture was cooled to -78 °C then treated with copper (I) bromide-dimethyl sulfide complex (67 mg, 0.33 mmol) and HMPA (1.7 mL, 9.82 mmol). A solution of acrolein (**305**) (459 μL, 6.87 mmol) and TMSCl (1.25 mL, 9.82 mmol) in THF (2 mL) was then added, dropwise *via* syringe pump, over 30 min. The reaction mixture was stirred at -78 °C for 4 h and then warmed up to 18 ºC and stirred at this temperature for a further 16 h. The reaction mixture was treated with triethylamine (5 mL) and water (20 mL) then extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with water (2 x 20 mL) and brine (20 mL) then concentrated under reduced pressure to give unstable *silyl enol ether **306*** as a clear, colourless oil. This material was used in the next step of the reaction sequence without purification.

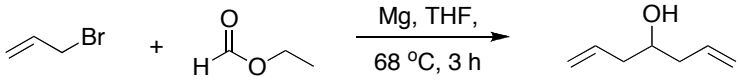
^{1}H NMR (300 MHz) δ 6.27 (dt, *J* = 11.9 and 1.2 Hz, 1H), 5.96 (dd, *J* = 9.8 and 5.8 Hz, 1H), 5.75 (m, 2H), 5.00 (m, 1H), 4.65 (dd, *J* = 8.9 and 3.8 Hz, 1H), 4.50 (d, *J* = 8.7 Hz, 1H), 2.80 (qd, *J* = 13.7 and 7.3 Hz, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 0.18 (s, 9H)

A solution of silyl enol ether **306** (129.1 mg, *ca*. 0.460 mmol) in THF (5 mL) was cooled to -78 ºC and treated with a solution of HF-pyridine/pyridine/THF (2:1:1, 0.1 mL, 1.28 mmol). The reaction mixture was stirred at this temperature for 2 h then treated with a solution of allyl magnesium bromide in ether (1.15 mL of a 2 M solution prepared from allyl bromide and magnesium, 2.30 mmol). After stirring at -78 ºC for 15 min the reaction mixture was allowed to slowly warm to 0 ºC and stirred for a further 1 h then poured into water (20 mL). The ensuing mixture was extracted with Et_2O (4 x 25 mL) and the combined organic fractions were washed with brine (25 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced

pressure. Purification of the ensuing yellow oil by flash column chromatography (silica, 3:7 *v/v* EtOAc/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.2, 3:7 *v/v* EtOAc/hexane), a *ca.* 1:1 mixture of the epimeric forms of the *title alcohol* ***308*** (15 mg, 13% over 3 steps) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.97 (dd, *J* = 9.5 and 5.6 Hz, 1H), 5.90–5.74 (m, 3H), 5.14 (m, 2H), 4.67 (dt, *J* = 8.8 and 3.2 Hz, 1H), 4.54 (dd, *J* = 8.5 and 6.1 Hz, 1H), 3.69 (m, 1H), 2.48–2.13 (m, 4H), 1.96 (br s, 1H), 1.82–1.57 (m, 2H), 1.40 (s, 3H), 1.39 (s, 1.5H), 1.38 (s, 1.5H).
^{13}C NMR (75 MHz) δ 138.0 (C), 137.7 (C), 134.7 (CH), 134.6 (CH), 124.6 (CH), 124.5 (CH), 122.8 (CH), 122.7 (CH), 118.8 (CH), 118.6 (CH), 118.2 (CH_2), 118.0 (CH_2), 105.2(5) (C), 105.1(8) (C), 73.5 (CH), 73.4 (CH), 71.3(3) (CH), 71.3(0) (CH), 70.4 (CH), 69.9 (CH), 42.0 (CH_2), 41.9 (CH_2), 34.3 (two overlapping signals, 2 x CH_2), 30.0 (CH_2), 29.6 (CH_2), 26.9 (CH_3), 26.8 (CH_3), 25.0 (CH_3), 24.9 (CH_3).
IR ν_{max} 3434, 3074, 3045, 2984, 2932, 1640, 1439, 1402, 1379, 1370, 1235, 1210, 1158, 1046, 916, 867, 717 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 235 [$(M - CH_3\cdot)^+$, 8%], 192 (87), 175 (30), 133 (72), 121 (21), 107 (100), 95 (29), 91 (59), 77 (59), 65 (22), 55 (29), 43 (75).
HREIMS Found: $(M - CH_3\cdot)^+$, 235.1330. $C_{15}H_{22}O_3$ requires $(M - CH_3\cdot)^+$, 235.1334.

Hepta-1,6-dien-4-ol (309)



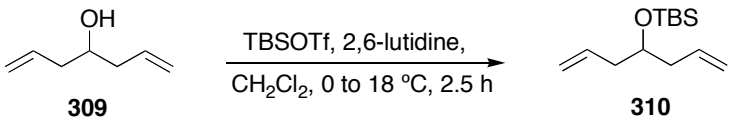
309a **309b** **309**

Following a procedure established by Hutchison *et al.*,[198] allyl bromide (**309a**) (*ca.* 20 drops) was added dropwise to a flask containing magnesium turnings (8.20 g, 0.34 mmol) and THF (20 mL) until initiation of the reaction was observed. A mixture of allyl bromide (28.6 mL, 0.33 mmol) and ethyl formate (**309b**) (13.0 mL, 0.16 mmol) in THF (145 mL) was then added *via* dropping funnel at a rate that maintained autoreflux of the reaction mixture. After the addition was completed the ensuing mixture was heated at reflux for 2 h then cooled to 0 °C and HCl (10 % aqueous solution) was added until the aqueous phase was acidic to litmus paper. The ensuing biphasic system was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic phases were washed with $NaHCO_3$ (20 mL of a saturated aqueous solution) and brine (20 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Distillation of this material gave hepta-1,6-dien-4-ol (**309**) (15.5 g, 85 %) as a clear, colourless liquid, b.p. = 150–151 °C.

^{1}H NMR (300 MHz) δ 5.83 (m, 2H), 5.14 (m, 4H), 3.70 (m, 1H), 2.24 (m, 4H), 1.83 (br d, *J* = 3.6 Hz, 1H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[198]

***tert*-Butyl[(1-allylbut-3-en-1-yl)oxy]dimethylsilane (310)**



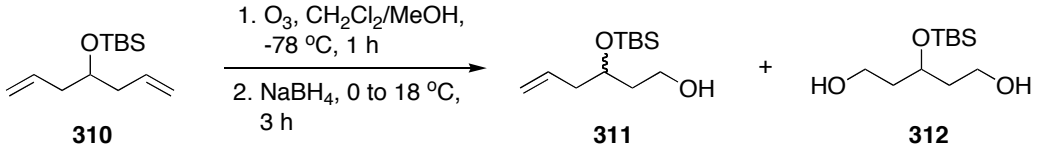
309 **310**

A solution of hepta-1,6-dien-4-ol (**309**) (10.0 mL, 0.08 mol) and 2,6-lutidine (16 mL, 0.14 mol) in CH_2Cl_2 (200 mL) was cooled to 0 °C then treated, dropwise, with TBSOTf (26.5 mL, 0.12 mol) over 30 min. The ensuing mixture was then allowed to warm to 18 °C and after stirring at this temperature for 2 h it was diluted with Et_2O (500 mL), washed with $NaHSO_4$ (100 mL of a saturated aqueous solution) and brine (100 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing clear, yellow liquid was comprised of a *ca*. 1:1.4 mixture of the desired silyl ether **310** and 2,6-lutidine. This mixture was used directly in the ozonolysis step with the lutidine serving to attenuate the reactivity of the ozone. For the purposes of characterization, a small sample of the mixture was subjected to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.8, 3:7 *v/v* EtOAc/hexane), the title silyl ether **310** as a clear, colourless liquid.

^{1}H NMR (300 MHz) δ 5.84 (m, 2H), 5.13 (m, 2H), 5.02 (m, 2H), 3.75 (qu, *J* = 5.9 Hz, 1H), 2.22 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[199]

3-{[*tert*-Butyl(dimethyl)silyl]oxy}hex-5-en-1-ol (311) and 3-{[*tert*-butyl(dimethyl)silyl]oxy}-pentane-1,5-diol (312)



310 **311** **312**

A mixture of silyl ether **310** (6.0 g, 26.5 mmol) and 2,6-lutidine (3.98 g, 37.1 mmol) in CH_2Cl_2/MeOH (60 mL of a 1:1 *v/v* mixture) was cooled to –78 °C then sparged with ozone generated using a 500 Model Fischer portable ozone-generator. After 1 h the stream of ozone was replaced with nitrogen then the reaction mixture was diluted with MeOH (30 mL) and warmed to 0 °C. Granular $NaBH_4$ (4.00 g, 0.12 mol) was then added in portions over 1 h (CAUTION - vigorous reaction). The resulting solution was carefully warmed to 18 °C and stirred at this temperature for a further 2 h. Water (30 mL) was then added to the reaction mixture and after 10 min the MeOH was removed under reduced pressure. The ensuing residue was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic fractions were washed with brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a colourless oil that was subjected to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane then 1:4 *v/v* MeOH/CH_2Cl_2 elution). In this manner three fractions, A, B and C, were obtained.

Concentration of fraction A (R_f = 0.8, 3:7 *v/v* EtOAc/hexane) afforded the starting silyl ether **310** (667 mg, 11% recovery) which was identical, in all respects, with authentic material.

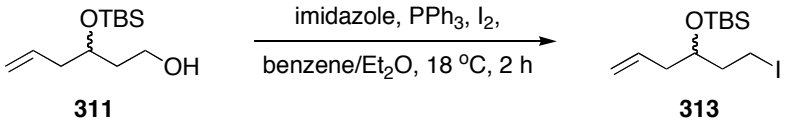
Concentration of fraction B (R_f = 0.5, 3:7 *v/v* EtOAc/hexane) afforded the *title alcohol **311*** (2.62 g, 48% at 89% conversion) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.78 (m, 1H), 5.08 (m, 1H), 5.03 (m, 1H), 3.97 (m, 1H), 3.80 (m, 1H), 3.70 (m, 1H), 2.52 (broad s, 1H), 2.30 (t, *J* = 7.08, 2H), 1.80 (m, 1H), 1.65 (m, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).
^{13}C NMR (75 MHz) δ 134.5 (CH), 117.3 (CH_2), 71.1 (CH), 60.0 (CH_2), 41.7 (CH_2), 37.7 (CH_2), 25.8 (CH_3), 17.9 (C), –4.4 (CH_3), –4.8 (CH_3).
IR ν_{max} 3350, 3077, 2954, 2930, 2887, 2857, 1641, 1472, 1463, 1434, 1413, 1361, 1255, 1071, 1027, 1005, 969, 938, 912, 836, 775, 666 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 231 [$(M + H)^+$, <1%], 189 [$(M – CH_2{=}CHCH_2{\cdot})^+$, 69], 185 (10), 173 (38), 145 (100), 131 (58), 127 (10), 119 (10), 115 (15), 105 (25).
HREIMS Found: $(M + H)^+$, 231.1780. $C_{12}H_{26}O_2Si$ requires $(M + H)^+$, 231.1780. Found: $(M – CH_2{=}CHCH_2{\cdot})^+$, 189.1314. $C_{12}H_{26}O_2Si$ requires $(M – CH_2{=}CHCH_2{\cdot})^+$, 189.1311.

Concentration of fraction C (R_f = 0.2, EtOAc) afforded *diol* ***312*** (2.86 g, 46% at 89% conversion) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 4.15 (qu, *J* = 5.9 Hz, 1H), 3.76 (m, 4H), 2.48 (broad s, 1H), 2.41 (broad s, 1H), 1.81 (m, 4H), 0.90 (s, 9H), 0.12 (s, 6H).
^{13}C NMR (75 MHz) δ 69.4 (CH), 59.7 (CH_2), 38.4 (CH_2), 25.8 (CH_3), 17.9 (CH), –4.7 (CH_3).
IR ν_{max} 3338, 2953, 2930, 2886, 2857, 1472, 1463, 1409, 1386, 1361, 1256, 1060, 1028, 1005, 865, 836, 775, 721, 664 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 235 [$(M + H)^+$, <1%], 189 (11), 159 (22), 147 (15), 131 (27), 105 (95), 75 (100), 67 (16), 55 (20), 43 (16).
HREIMS Found: $(M + H)^+$, 235.1727. $C_{11}H_{26}O_3Si$ requires $(M + H)^+$, 235.1729.

***tert*-Butyl{[1-(2-iodoethyl)but-3-en-1-yl]oxy}dimethylsilane (313)**



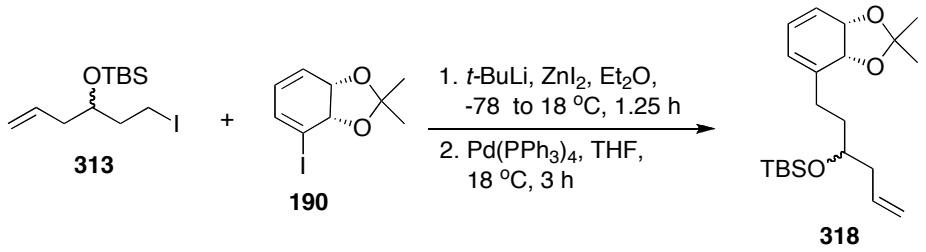
311 **313**

A vigorously stirred solution of alcohol **311** (2.32 g, 10.1 mmol), triphenylphosphine (4.21 g, 16.1 mmol) and imidazole (1.10 g, 16.1 mmol) in benzene/Et_2O (75 mL of a 1:2 *v/v* mixture) was treated with molecular iodine (4.08 g, 16.1 mmol). After 2 h at 18 °C the reaction mixture was diluted with Et_2O (200 mL) then washed with $Na_2S_2O_3$ (100 mL of a saturated aqueous solution) and brine (100 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was redissolved in a minimal amount of hexane and left to stand at 18 °C overnight. The triphenylphosphine oxide thus formed was filtered off and washed with hexane (3 × 20 mL). The combined filtrates were concentrated under reduced pressure and the residual oil subjected to flash column chromatography (silica, hexane elution). Concentration of the appropriate fractions (R_f = 0.6, 1:9 *v/v* EtOAc/hexane) afforded the *title iodide* ***313*** (2.6 g, 75%) as a clear, pale-yellow oil.

^{1}H NMR (300 MHz) δ 5.78 (m, 1H), 5.08 (m, 1H), 5.03 (m, 1H), 3.80 (qu, *J* = 5.9 Hz, 1H), 3.21 (m, 2H), 2.24 (t, *J* = 6.5 Hz, 2H), 1.95 (m, 2H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).
^{13}C NMR (75 MHz) δ 134.2 (CH), 117.5 (CH_2), 71.6 (CH), 41.6 (CH_2), 40.5 (CH_2), 25.8 (CH_3), 18.0 (C), 3.3 (CH_2), –4.3 (CH_3), –4.5 (CH_3).
IR ν_{max} 2955, 2929, 2894, 2857, 1641, 1471, 1462, 1434, 1361, 1256, 1218, 1170, 1141, 1064, 1003, 943, 916, 835, 811, 775, 667 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 339 [$(M – H\cdot)^+$, <1%], 299 [$(M – CH_2{=}CHCH_2\cdot)^+$, 78], 283 (100), 255 (82), 215 (27), 185 (51), 155 (27), 127 (51), 115 (39), 99 (45), 81 (65), 73 (99).

HREIMS Found: $(M - H\cdot)^+$, 339.0627. $C_{12}H_{25}O^{127}ISi$ requires $(M - H\cdot)^+$, 339.0641. Found: $(M - CH_2{=}CHCH_2\cdot)^+$, 299.0339. $C_{12}H_{25}O^{127}ISi$ requires $(M - CH_2{=}CHCH_2\cdot)^+$, 299.0328.

***tert*-Butyl[(1-{2-[(3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxol-4-yl]ethyl}but-3-en-1-yl)oxy]dimethylsilane (318)**



A stirred solution of iodide **313** (1.89 g, 5.55 mmol) in Et_2O (28 mL) was cooled to –78 °C and *t*-BuLi (7.18 mL of a 1.7 M solution in pentane, 12.2 mmol) was added dropwise over 4 min. After 3 min of further stirring a solution of anhydrous ZnI_2 (1.95 g, 6.10 mmol) in THF (6.1 mL) was added. The ensuing mixture was stirred at –78 °C for a further 15 min then allowed to warm to 18 °C over 1 h. A solution of vinyl iodide **190** (1.54 g, 5.55 mmol) and $Pd(PPh_3)_4$ (64 mg, 0.56 mmol) in THF (5.6 mL) was then added dropwise to give an initially pale-yellow reaction mixture. After stirring for 3 h the by now bright-yellow coloured reaction mixture was quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to a yellow oil. Subjection of this material to flash column chromatography (silica, 1:99 → 1:19 *v/v* EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.4, 1:9 *v/v* EtOAc/hexane) afforded a *ca*. 1:1 mixture of the epimeric forms of the *title compound* ***318*** (1.52 g, 75%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.70 (dd, *J* = 9.5 and 5.6 Hz, 1H), 5.89–5.74 (complex m, 2H), 5.71 (d, *J* = 5.6 Hz, 1H), 5.06 (d, *J* = 6.3 Hz, 1H), 5.01 (s, 1H), 4.65 (dd, *J* = 8.8 and 3.9 Hz, 1H), 4.51 (dd, *J* = 8.8 and, 4.2 Hz, 1H), 3.75 (m, 1H), 2.27 (m, 4H), 1.64 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (75 MHz) δ 138.8 (C), 138.7 (C), 135.2 (two signals overlapping, 2 x CH), 124.7 (two signals overlapping, 2 x CH), 122.7 (two signals overlapping, 2 x CH), 118.2 (CH), 118.1 (CH), 116.8 (two signals overlapping, 2 x CH_2), 105.3 (two signals overlapping, 2 x C), 73.6 (CH), 73.5 (CH), 71.7 (CH), 71.6 (CH), 71.4 (two signals overlapping, 2 x CH), 41.9 (CH_2), 41.7 (CH_2), 34.3 (two signals overlapping, 2 x CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.9 (two signals overlapping, 2 x CH_3), 25.8 (two signals overlapping, 2 x CH_3), 25.1 (two signals overlapping,

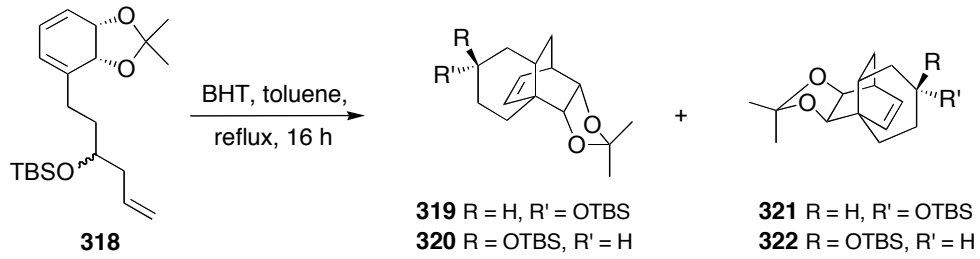
2 x CH_3), 18.1 (two signals overlapping, 2 x C), –4.3 (two signals overlapping, 2 x CH_3), –4.5 (two signals overlapping, 2 x CH_3).

IR ν_{max} 2982, 2953, 2930, 2886, 2857, 1641, 1472, 1462, 1378, 1369, 1254, 1208, 1159, 1083, 1067, 1005, 912, 869, 835, 774, 725, 666 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 364 ($M^{+\bullet}$, <1%), 349 (5), 307 (8), 306 (7), 249 (37), 231 (40), 207 (31), 181 (100), 171 (31), 133 (84), 107 (41), 75 (71), 73 (72).

HREIMS Found: $M^{+\bullet}$, 364.2443. $C_{21}H_{36}O_3Si$ requires $M^{+\bullet}$, 364.2434.

***tert*-Butyl{[(3a*S*,4*R*,5a*S*,7*S*,9a*S*,9b*R*)-2,2-dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2-*d*][1,3]dioxol-7-yl]oxy}dimethylsilane (319), *tert*-butyl{[(3a*S*,4*R*,5a*S*,7*R*,9a*S*,9b*R*)-2,2-dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2-*d*][1,3]dioxol-7-yl]oxy}dimethylsilane (320), *tert*-butyl{[(3a*S*,4*S*,5a*R*,7*R*,9a*R*,9b*R*)-2,2-dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2-*d*][1,3]dioxol-7-yl]oxy}dimethylsilane (321) and *tert*-butyl{[(3a*S*,4*S*,5a*R*,7*S*,9a*R*,9b*R*)-2,2-dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2-*d*][1,3]dioxol-7-yl]oxy}dimethylsilane (322)**



318

319 R = H, R' = OTBS
320 R = OTBS, R' = H

321 R = H, R' = OTBS
322 R = OTBS, R' = H

A solution of diene **318** (3.30 g, 9.10 mmol) and BHT (75 mg, 0.34 mmol) in toluene (600 mL) was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the ensuing yellow oil subjected to flash column chromatography (silica, 1:99 → 1:19 *v/v* EtOAc/hexane gradient elution) and thus affording three fractions, A, B and C.

Concentration of fraction A (R_f = 0.4, 1:9 *v/v* EtOAc/hexane) afforded the *title compound* ***319*** (128 mg, 4%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.21 (t, *J* = ~8.3 Hz, 1H), 5.91 (d, *J* = 8.3 Hz, 1H), 4.09 (ddd, *J* = 8.3, 4.2 and 1.0 Hz, 1H), 3.91 (broad s, 1H), 3.63 (d, *J* = 8.3 Hz, 1H), 2.68 (m, 1H), 2.48 (m, 1H), 2.28–2.06 (complex m, 3H), 1.68–1.25 (complex m, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 1.00 (m, 1H), 0.90 (s, 9H), 0.47 (m, 1H), 0.02(0) (s, 3H), 0.01(6) (s, 3H).

^{13}C NMR (75 MHz) δ 135.2 (CH), 132.9 (CH), 111.6 (C), 80.2 (CH), 75.7 (CH), 66.4 (CH), 42.2 (C), 40.1 (CH_2), 34.8 (CH), 30.2 (CH_2), 27.1 (CH_2), 26.2 (CH_3), 25.8 (CH_3), 24.7 (CH_3), 24.6 (CH_2), 23.5 (CH), 18.0 (C), –4.8 (CH_3), –4.9 (CH_3).

IR ν_{max} 2951, 2928, 2858, 1472, 1462, 1446, 1379, 1371, 1259, 1207, 1165, 1143, 1119, 1100, 1088, 1062, 978, 966, 884, 864, 836, 809, 772, 706, 688, 645 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 364 ($M^{+\bullet}$, <1%), 349 (7), 307 (9), 275 (11), 249 (61), 231 (47), 205 (58), 174 (51), 157 (91), 145 (41), 131 (100), 117 (31), 101 (62), 91 (60), 75 (78), 57 (31).

HREIMS Found: $M^{+\bullet}$, 364.2427. $C_{21}H_{36}O_3Si$ requires $M^{+\bullet}$, 364.2434.

Optical Rotation $[\alpha]_D$ = +33 (*c* 0.2, $CHCl_3$).

Concentration of fraction B [R_f = 0.3(7), 1:9 *v/v* EtOAc/hexane] afforded a 5:1 and inseparable mixture of the *title compounds* ***320*** and ***321*** (1.58 g, 48%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ (**320**, major isomer) 6.11 (t, *J* = 8.0 and 6.6 Hz, 1H), 5.84 (dd, *J* = 8.3 and 1.0 Hz, 1H), 4.18 (ddd, *J* = 7.3, 3.2 and 1.0 Hz, 1H), 3.93 (qu, *J* = 2.4 Hz, 1H), 3.80 (dd, *J* = 7.3 and 1.2 Hz, 1H), 2.69 (m, 1H), 1.87–1.38 (complex m, 7H), 1.32 (s, 3H), 1.27 (s, 3H), 1.10–0.82 (complex m, 1H), 0.89 (s, 9H), 0.69 (m, 1H), 0.03 (s, 3H), 0.02 (s, 3H); (**321**, minor isomer) 6.20 (dd, *J* = 8.0 and 6.6 Hz, 1H), 5.89 (d, *J* = 8.3 Hz, 1H), 4.07 (ddd, *J* = 8.3, 4.2 and 1.2 Hz, 1H), 3.68 (d, *J* = 8.3 Hz, 1H), 3.52 (tt, *J* = 10.7 and 4.2 Hz, 1H), 2.69 (m, 1H), 2.23 (ddd, *J* = 12.0, 9.3 and 2.4 Hz, 1H), 1.98 (m, 1H), 1.87–1.38 (complex m, 5H), 1.32 (s, 3H), 1.27 (s, 3H), 1.10–0.82 (complex m, 1H), 0.87 (s, 9H), 0.58 (m, 1H), 0.05 (s, 3H), 0.04 (s, 3H).

IR ν_{max} 2930, 2884, 2860, 1472, 1462, 1370, 1251, 1207, 1167, 1081, 1065, 1036, 1020, 976, 869, 836, 774, 725, 699, 682 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 364 ($M^{+\bullet}$, 3%), 349 (45), 249 (58), 231 (31), 205 (21), 174 (95), 173 (80), 157 (61), 145 (71), 132 (90), 131 (100), 117 (34), 101 (35), 91 (65), 75 (93), 73 (50), 59 (21), 43 (28).

HREIMS Found: $M^{+\bullet}$, 364.2437. $C_{21}H_{36}O_3Si$ requires $M^{+\bullet}$, 364.2434.

Concentration of fraction C (R_f = 0.3, 1:9 *v/v* EtOAc/hexane) afforded the *title compound* ***322*** (1.47 g, 45%) as a white, crystalline solid, m.p. = 119–121 °C.

^{1}H NMR (300 MHz) δ 6.09 (dd, *J* = 7.8 and 6.8 Hz, 1H), 5.80 (dd, *J* = 8.3 and 1.0 Hz, 1H), 4.16 (ddd, *J* = 7.1, 3.2 and 0.7 Hz, 1H), 3.70 (dd, *J* = 7.3 and 1.2 Hz, 1H), 3.49 (m, 1H), 2.71 (m, 1H), 2.11 (dt, *J* = 10.0 and 3.2 Hz, 1H), 1.81 (m, 1H), 1.64 (m, 2H), 1.49–1.17 (partially obscured m, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 0.98 (partially obscured m, 1H), 0.87 (s, 9H), 0.79 (m, 1H), 0.04(3) (s, 3H), 0.03(7) (s, 3H).

^{13}C NMR (75 MHz) δ 132.5 (CH), 130.3 (CH), 108.3 (C), 84.1 (CH), 79.4 (CH), 71.1 (CH), 41.7 (CH_2), 41.3 (C), 34.6 (CH), 34.0 (CH), 32.2 (CH_2), 30.4 (CH_2), 29.4 (CH_2), 25.9 (CH_3), 25.5 (CH_3), 24.9 (CH_3), 18.2 (C), –4.5(8) (CH_3), –4.6(1) (CH_3).

IR ν_{max} 2931, 2882, 2858, 1472, 1461, 1450, 1377, 1277, 1249, 1207, 1167, 1100, 1082, 1067, 1042, 1005, 994, 887, 871, 836, 805, 774, 726, 699, 668 cm^{-1}.

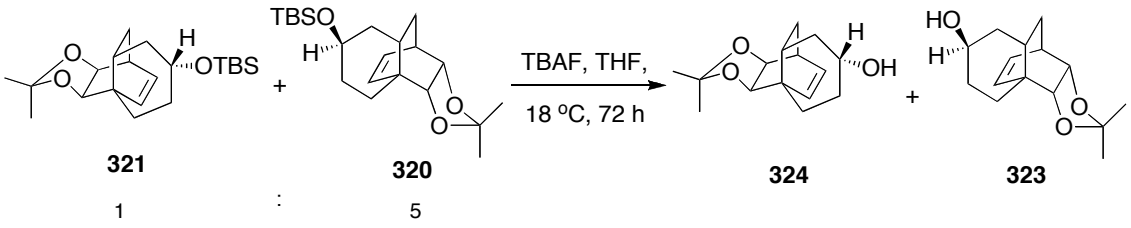
Mass spectrum (EI, 70 eV) *m/z* 364 ($M^{+\bullet}$, <<1%), 363 [$(M - H^{\bullet})^+$, <1], 349 (27), 307 (35), 249 (86), 174 (72), 157 (71), 145 (39), 132 (65), 131 (94), 117 (29), 105 (34), 91 (65), 75 (100).

HRIEMS Found: $M^{+\bullet}$, 364.2437. $C_{21}H_{36}O_3Si$ requires $M^{+\bullet}$, 364.2434.

Elemental Analysis Found: C, 69.43; H, 10.06. $C_{21}H_{36}O_3Si$ requires C, 69.18; H, 9.95%.

Optical Rotation $[\alpha]_D$ = +15 (*c* 1.0, $CHCl_3$).

(3a*S*,4*S*,5a*R*,7*R*,9a*R*,9b*R*)-2,2-Dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2-*d*][1,3]dioxol-7-ol (324) and (3a*S*,4*R*,5a*S*,7*R*,9a*S*,9b*R*)-2,2-dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2-*d*][1,3]dioxol-7-ol (323)



A solution of a 5:1 mixture of silyl ethers **320** and **321** (1.59 g, 4.37 mmol) in THF (15 mL) was treated with tetra-*n*-butylammonium fluoride (10 mL of a 1.0 M solution in THF, 10 mmol) and the ensuing mixture was stirred at 18 °C for 72 h. The reaction mixture was then concentrated under reduced pressure and the brown residue so obtained was subjected to flash column chromatography (silica, 1:99 → 1:19 *v/v* EtOAc/hexane gradient elution) thus giving two fractions, A and B.

Concentration of fraction A (R_f = 0.3, 1:1 *v/v* EtOAc/hexane) afforded the *alcohol derived from ether **324*** (130 mg, 12%) as a white, crystalline solid, m.p. = 80–82 °C.

^{1}H NMR (300 MHz) δ 6.21 (dd, *J* = 8.2 and 6.7 Hz, 1H), 5.87 (d, *J* = 8.1 Hz, 1H), 4.06 (ddd, *J* = 8.2, 4.1 and 1.1 Hz, 1H), 3.67 (d, *J* = 8.2 Hz, 1H), 3.53 (m, 1H), 2.67 (m, 1H), 2.22 (ddd, *J* = 12.2, 9.3 and 2.6 Hz, 1H), 2.05–1.86 (complex m, 2H), 1.76 (broad s, 1H), 1.72–1.55 (complex m, 3H), 1.47 (s, 3H), 1.37 (m, 1H, partially obscured), 1.29 (s, 3H), 0.90 (q, *J* = 12.5 Hz, 1H), 0.57 (dm, *J* = 11.0 Hz, 1H).

^{13}C NMR (75 MHz) δ 135.0 (CH), 132.7 (CH), 111.5 (C), 79.1 (CH), 75.5 (CH), 69.8 (CH), 41.7 (CH_2), 41.4 (C), 34.7 (CH), 32.0 (CH_2), 29.1 (CH), 28.9 (CH_2), 26.8 (CH_2), 26.3 (CH_3), 24.4 (CH_3).

IR ν_{max} 3369, 2986, 2929, 2860, 1448, 1380, 1372, 1262, 1207, 1167, 1061, 1021, 992, 882, 863, 708, 645, 524 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 6%), 235 [$(M - CH_3\bullet)^+$, 19], 192 (21), 174 (100), 157 (46), 150 (68), 145 (91), 131 (78), 117 (48), 101 (78), 91 (99), 43 (48).

HREIMS Found: $M^{+\bullet}$, 250.1573. $C_{15}H_{22}O_3$ requires $M^{+\bullet}$, 250.1569.

Optical Rotation $[\alpha]_D$ = +32 (*c* 1.4, $CHCl_3$).

Concentration of fraction B [R_f = 0.2(6), 1:1 *v/v* EtOAc/hexane] afforded the *title compound* ***323*** (827 mg, 76%) as a white, crystalline solid, m.p. = 134–135 °C.

^{1}H NMR (300 MHz) δ 6.12 (dd, *J* = 8.0 and 6.6 Hz, 1H), 5.83 (d, *J* = 8.0 Hz, 1H), 4.17 (ddd, *J* = 7.3, 3.3 and 1.0 Hz, 1H), 4.01 (broad t, *J* = 2.3 Hz, 1H), 3.81 (dd, *J* = 7.3 and 1.1 Hz, 1H), 2.72 (m, 1H), 1.90 (m, 1H), 1.78–1.56 (complex m, 6H), 1.41 (s, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.70 (m, 1H), 0.72 (m, 1H).

^{13}C NMR (75 MHz) δ 131.8 (CH), 131.0 (CH), 108.2 (C), 83.9 (CH), 79.3 (CH), 66.1 (CH), 41.7 (C), 38.4 (CH_2), 34.4 (CH), 29.1 (CH_2), 28.9 (CH_2), 27.8 (CH), 25.6 (CH_2), 25.5 (CH_3), 24.9 (CH_3).

IR ν_{max} 3472, 2984, 2977, 2932, 2885, 2858, 1454, 1378, 1370, 1277, 1257, 1231, 1206, 1163, 1076, 1054, 1013, 927, 881, 822, 725, 701, 601 cm^{-1}.

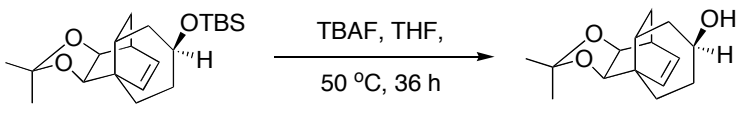
Mass spectrum (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 5%), 235 [$(M - CH_3^\bullet)^+$, 41], 192 (49), 174 (100), 157 (22), 145 (72), 131 (79), 117 (40), 104 (51), 91 (90), 85 (27), 77 (26), 43 (48).

HREIMS Found: $M^{+\bullet}$, 250.1562. $C_{15}H_{22}O_3$ requires $M^{+\bullet}$, 250.1569.

Elemental Analysis Found: C, 71.83; H, 8.62. $C_{15}H_{22}O_3$ requires C, 71.97; 8.86%.

Optical Rotation $[\alpha]_D$ = +29 (*c* 1.1, $CHCl_3$).

(3a*S*,4*S*,5a*R*,7*S*,9a*R*,9b*R*)-2,2-Dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2*d*][1,3]dioxol-7-ol (325)



322 **325**

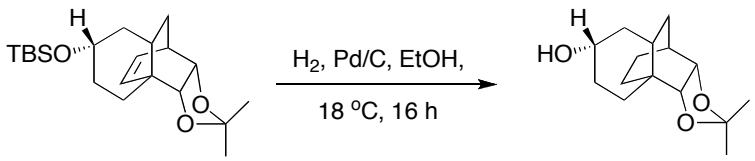
A solution of silyl ether **322** (99 mg, 0.27 mmol) in THF (2 mL) was treated with tetra-*n*-butylammonium fluoride (1 mL of a 1.0 M solution in THF, 1 mmol) and the ensuing mixture

was warmed to 50 °C then stirred at this temperature for 24 h. After this time, an additional aliquot of tetra-*n*-butylammonium fluoride (1 mL of a 1.0 M solution in THF, 1 mmol) was added and the reaction mixture was stirred at 40 °C for a further 24 h then concentrated under reduced pressure. The brown residue thus obtained was subjected to flash column chromatography (silica, 3:7 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3, 1:1 *v/v* EtOAc/hexane) afforded the *title alcohol* ***325*** (58.0 mg, 85%) as a white, crystalline solid, m.p. = 115–116 °C.

^{1}H NMR (300 MHz) δ 6.23 (dd, *J* = 8.3 and 6.8 Hz, 1H), 5.92 (d, *J* = 8.3 Hz, 1H), 4.07 (dd, *J* = 8.3 and 3.9 Hz, 1H), 3.96 (qu, *J* = 2.9 Hz, 1H), 3.66 (d, *J* = 8.3 Hz, 1H), 2.68 (m, 1H), 2.37 (m 1H), 2.23 (ddd, *J* = 12.2, 9.5 and 2.7 Hz, 1H), 2.00 (td, *J* = 12.2 and 4.6 Hz, 1H), 1.81–1.53 (complex m, 4H), 1.51 (s, 3H), 1.43 (dt, *J* = 13.7 and 3.7 Hz, 1H), 1.31 (s, 3H), 1.12 (td, *J* = 13.7 and 2.7 Hz, 1H), 0.51 (dt, *J* = 12.5 and 2.9 Hz, 1H).
^{13}C NMR (75 MHz) δ 134.5 (CH), 133.2 (CH), 111.6 (C), 79.8 (CH), 75.6 (CH), 66.3 (CH), 42.0 (C), 38.9 (CH_2), 34.8 (CH), 29.3 (CH_2), 26.6 (CH_2), 26.4 (CH_3), 24.5(1) (CH_2), 24.5(5) (CH_3), 23.8 (CH).
IR ν_{max} 3432, 3038, 2976, 2919, 2861, 1446, 1379, 1372, 1262, 1207, 1166, 1062, 1009, 972, 884, 866, 705 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 3%), 235 [$(M - CH_3^{\bullet})^+$, 17], 192 (16), 174 (82), 157 (38), 145 (90), 131 (79), 117 (41), 101 (100), 91 (90), 77 (25), 43 (39).
HREIMS Found: $M^{+\bullet}$, 250.1570. $C_{15}H_{22}O_3$ requires $M^{+\bullet}$, 250.1569.
Elemental Analysis Found: C, 71.80; H, 8.91. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%.
Optical Rotation $[\alpha]_D$ = +29 (*c* 1.4, $CHCl_3$).

(3a*S*,4*S*,5a*S*,7*S*,9a*S*,9b*R*)-2,2-Dimethyloctahydro-4*H*-4,9a-ethanonaphtho[1,2-*d*][1,3]-dioxol-7-ol (327)

Method 1:



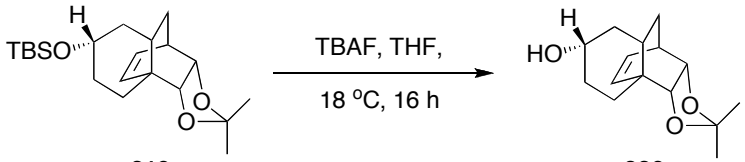
319 **327**

A solution of alkene **319** (1.51 g, 4.14 mmol) in EtOH (80 mL) was treated with 10% palladium on carbon (1.20 g) and the resulting suspension was stirred at 18 °C under a hydrogen atmosphere (1 atm) for 16 h. The reaction mixture was then filtered through a *ca*. 5 cm deep pad

of Celite^{TM} and the solids thus retained were washed with EtOH (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL). The combined filtrates were concentrated under reduced pressure to give the *title alcohol **327*** (1.02 g, 98%) as a white, crystalline solid (R_f = 0.1, 3:7 *v/v* EtOAc/hexane), m.p. = 120–121 °C.

^{1}H NMR (300 MHz) δ 4.13 (m, *J* = 8.3 Hz, 1H), 3.60 (dd, *J* = 8.3 and 1.7 Hz, 1H), 3.50 (m, 1H), 1.99–1.55 (complex m, 8H), 1.51 (s, 3H), 1.43–1.07 (complex m, 7H), 1.35 (s, 3H).
^{13}C NMR (75 MHz) δ 108.1 (C), 82.3 (CH), 76.2 (CH), 70.5 (CH), 39.3 (CH_2), 33.3(8) (C), 33.3(6) (CH), 32.9 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 29.1 (CH), 25.8 (CH_3), 24.1 (CH_3), 18.8 (CH_2), 17.2 (CH_2).
IR ν_{max} 3413, 3366, 2986, 2928, 2863, 1470, 1447, 1379, 1371, 1260, 1207, 1164, 1064, 1023, 963, 891, 877 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 251 [$(M - H\cdot)^+$, <1%], 237 [$(M - CH_3^{\bullet})^+$, 90], 219 (15), 177 (45), 159 (100), 131 (89), 117 (43), 105 (31), 91 (69), 79 (49), 67 (32), 43 (54).
HREIMS Found: $(M - CH_3\cdot)^+$, 237.1491. $C_{15}H_{24}O_3$ requires $(M - CH_3\cdot)^+$, 237.1491.
Elemental Analysis Found: C, 71.21; H, 9.43. $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.59%.
Optical Rotation $[\alpha]_D$ = –51 (*c* 1.4, $CHCl_3$).

Method 2: [*via* **(3a*S*,4*R*,5a*S*,7*S*,9a*S*,9b*R*)-2,2-dimethyloctahydro-4*H*-4,9a-ethenonaphtho[1,2-*d*][1,3]d ioxol-7-ol (326)**]



319 **326**

A solution of silyl ether **319** (91 mg, 0.25 mmol) in THF (2 mL) was treated with tetra-*n*-butylammonium fluoride (1 mL of a 1.0 M solution in THF, 1 mmol) and the ensuing mixture stirred at 18 °C for 16 h. The reaction mixture was then concentrated under reduced pressure and the brown residue thus obtained subjected to flash column chromatography (silica, 1:1 *v/v* EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.3, 1:1 *v/v* EtOAc/hexane) afforded the *title alcohol **326*** (65 mg, 97%) as a white, crystalline solid, m.p. = 91–93 °C.

^{1}H NMR (300 MHz) δ 6.12 (broadened dd, *J* = 8.3 and 6.8 Hz, 1H), 5.80 (dd, *J* = 8.3 and 1.0 Hz, 1H), 4.17 (ddd, *J* = 7.1, 3.2 and 1.0 Hz, 1H), 3.71 (dd, *J* = 7.1 and 1.2 Hz, 1H), 3.53 (m, 1H), 2.72 (m, 1H), 2.14 (m, 1H), 1.93 (m, 1H), 1.76 (m, 1H), 1.66 (ddd, *J* = 13.1, 9.3 and 2.4

Hz, 1H), 1.58 (broad s, 1H), 1.45–1.19 (complex m, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 0.93 (q, J = 12.5 Hz, 1H), 0.80 (ddd, J = 12.5, 4.6 and 3.2 Hz, 1H).

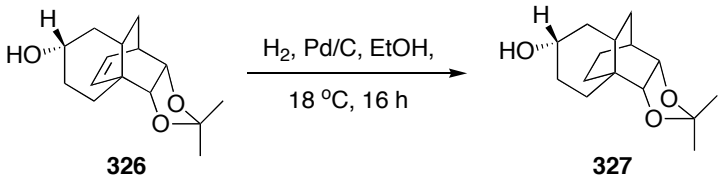
^{13}C NMR (75 MHz) δ 132.3 (CH), 130.6 (CH), 108.3 (C), 83.9 (CH), 79.3 (CH), 70.3 (CH), 41.3 (C), 41.2 (CH_2), 34.6 (CH), 33.9 (CH), 31.9 (CH_2), 30.3 (CH_2), 29.2 (CH_2), 25.5 (CH_3), 24.9 (CH_3).

IR ν_{max} 3408, 2981, 2930, 2863, 1451, 1372, 1245, 1205, 1166, 1062, 999, 885, 726, 699 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 250 ($M^{+\bullet}$, 8%), 235 (50), 192 (45), 174 (93), 145 (79), 131 (80), 117 (49), 100 (50), 91 (100), 77 (43), 43 (79).

HRIEMS Found: $M^{+\bullet}$, 250.1562. $C_{15}H_{22}O_3$ requires $M^{+\bullet}$, 250.1569.

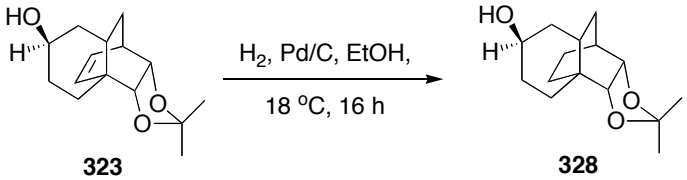
Optical Rotation $[\alpha]_D$ = +11 (*c* 1.05, $CHCl_3$).



326 **327**

A solution of alkene **326** (30 mg, 0.120 mmol) in EtOH (5 mL) was treated with 10% palladium on carbon (10 mg) and the resulting suspension stirred at 18 °C under a hydrogen atmosphere (1 atm) for 16 h. The reaction mixture was then filtered through a *ca.* 1 cm deep pad of Celite™ and the solids thus retained were washed with EtOH (2 × 5 mL) and CH_2Cl_2 (2 × 5 mL). The combined filtrates were concentrated under reduced pressure to give the title alcohol **327** (30.0 mg, 99%) as a white, crystalline solid. This material was identical, in all respects, to that obtained *via* Method 1 detailed immediately above.

(3a*S*,4*S*,5a*S*,7*R*,9a*S*,9b*R*)-2,2-Dimethyloctahydro-4*H*-4,9a-ethanonaphtho[1,2-*d*][1,3]dioxol-7-ol (328)



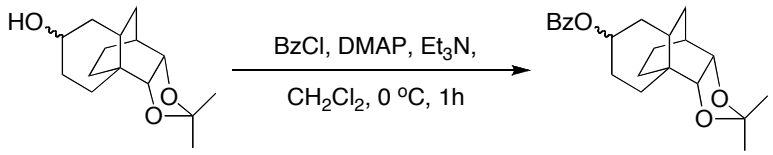
323 **328**

A solution of alkene **323** (0.87 g, 3.46 mmol) in EtOH (70 mL) was treated with 10% palladium on carbon (1.0 g) and the resulting suspension was stirred at 18 °C under a hydrogen atmosphere (1 atm) for 16 h. The reaction mixture was filtered through a pad of Celite™ (approx 5 cm thick) and the retained solids were washed with EtOH (2 x 20 mL) and CH_2Cl_2 (2 x 20 mL). The combined filtrates were concentrated under reduced pressure to give *title alcohol*

328 (0.87 g, 99%) as a white crystalline solid, (R_f = 0.1, 3:7 *v/v* EtOAc/hexane elution), m.p. = 131–132 °C.

^{1}H NMR (300 MHz) δ 4.13 (dd, *J* = 8.3 and 3.4 Hz, 1H), 4.05 (br s, 1H), 3.69 (d, *J* = 8.3 Hz, 1H), 1.89–1.29 (complex m, 13H), 1.53 (s, 3H), 1.35 (s, 3H), 1.19 (m, 1H), 1.00 (m, 1H)
^{13}C NMR (75 MHz) δ 108.1 (C), 82.2 (CH), 76.2 (CH), 66.2 (CH), 36.8 (CH_2), 33.8 (C), 30.8 (CH_2), 29.0 (CH), 28.2 (CH_2), 27.7 (CH_2), 27.3 (CH), 25.8 (CH_3), 24.1 (CH_3), 19.0 (CH_2), 16.5 (CH_2)
IR ν_{max} 3476, 2986, 2978, 2948, 2922, 2885, 2865, 1468, 1455, 1379, 1373, 1262, 1207, 1160, 1053, 1036, 997, 876 cm^{-1}
Mass spectrum (EI, 70 eV) 237 [$(M - CH_3^{\bullet})^+$, 100], 177 (15), 159 (88), 131 (51), 117 (19), 105 (15), 91 (31), 79 (20), 67 (16), 55 (14), 43 (25)
HREIMS Found: $(M - CH_3\cdot)^+$, 237.1492. $C_{15}H_{24}O_3$ requires $(M - CH_3\cdot)^+$, 237.1491
Elemental Analysis Found: C, 71.18; H, 9.34. $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.59%
Optical Rotation $[\alpha]_D$ = -29 (*c* 0.7, $CHCl_3$)

(3a*S*,4*S*,5a*S*,9a*S*,9b*R*)-2,2-Dimethyloctahydro-4*H*-4,9a-ethanonaphtho[1,2-*d*][1,3]dioxol-7-yl benzoate (239)



327 + 328 **329**

A solution of a *ca*. 1:1 mixture of alcohols **327** and **328** (1.50 g, 5.94 mmol), triethylamine (3.3 mL, 23.7 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (2.9 g, 23.7 mmol) in CH_2Cl_2 (60 mL) was cooled to 0 °C and treated with benzoyl chloride (2.0 mL, 17.2 mmol). The ensuing mixture was stirred at 0 °C for 1 h then $NaHCO_3$ (20 mL of a saturated aqueous solution) was added and the biphasic system so-formed was warmed to 18 °C and stirred at this temperature for 30 min. CH_2Cl_2 (40 mL) was then added and the separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were washed with brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure onto silica (*ca.* 4 g, 230–400 mesh). The ensuing free-flowing solid was subjected to flash column chromatography (1:9 → 1:4 *v/v* EtOAc/hexane gradient elution) to afford, after concentration of the appropriate fractions, a *ca*. 1:1 mixture of the epimeric forms of *benzoate **329*** (2.01 g, 95%) as a clear, colourless and viscous oil (R_f = 0.2, 1:9 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 8.04 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 5.27 (broad s, 0.5H), 4.85 (m, 0.5H), 4.15 (m, 1H), 3.73 (dd, *J* = 8.2 and 1.4 Hz, 0.5H), 3.64 (d, *J* = 8.2 Hz, 0.5H), 2.15–1.02 (complex m, 14H), 1.54 (s, 1.5H), 1.52 (s, 1.5H), 1.37 (s, 1.5H), 1.36 (s, 1.5H).

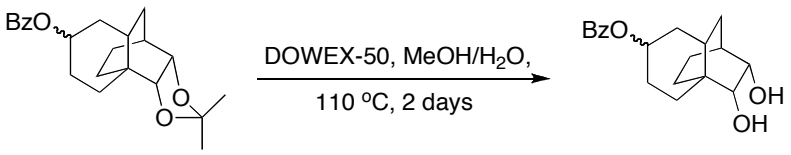
^{13}C NMR (75 MHz) δ 166.0 (C), 165.7 (C), 132.7 (two signals overlapping, 2 x CH), 130.9 (C), 130.7 (C), 129.4(9) (CH), 129.4(6) (CH), 128.3 (CH), 128.2 (CH), 108.1(9) (C), 108.1(6) (C), 82.3 (CH), 82.1 (CH), 76.1 (two signals overlapping, 2 x CH), 73.4 (CH), 70.2 (CH), 35.3 (CH_2), 33.9 (CH_2), 33.6 (C), 33.4 (C), 33.3 (CH), 32.7 (CH_2), 30.7 (two signals overlapping, 2 x CH_2), 29.3 (CH_2), 29.0(0) (CH), 28.9(5) (CH), 28.6 (CH), 26.6 (CH_2), 25.8(2) (CH_3), 25.7(9) (CH_3), 25.0 (CH_2), 24.2 (CH_3), 24.1 (CH_3), 18.9(5) (CH_2), 18.9(0) (CH_2), 17.1 (CH_2), 16.6 (CH_2).

IR ν_{max} 2985, 2934, 2864, 1715, 1450, 1379, 1314, 1274, 1206, 1113, 1066, 1026, 877 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 341 [$(M - CH_3\cdot)^+$, 100], 219 (28), 159 (82), 131 (36), 105 (65), 91 (25), 77 (31), 43 (19).

HREIMS Found: $(M - CH_3\cdot)^+$, 341.1756. $C_{22}H_{28}O_4$ requires $(M - CH_3\cdot)^+$, 341.1753.

(2*S*,3*S*,4*R*,4a*S*,8a*S*)-3,4-Dihydroxyoctahydro-2*H*-2,4a-ethanonaphthalen-7-yl benzoate (330)



329 **330**

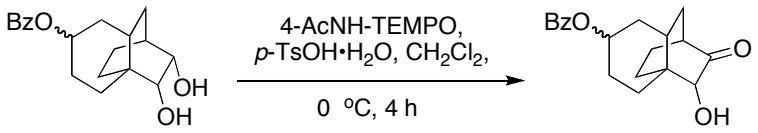
A solution of a *ca*. 1:1 mixture of the epimeric forms of acetonide **329** (1.00 g, 2.81 mmol) in MeOH/water (24 mL of a 5:1 *v/v* mixture) was treated with DOWEX-50 resin [1.0 g, activated by sequential washing with $NaHCO_3$ (saturated aqueous solution), water, 1 M aqueous HC1 then water]. The ensuing mixture was heated at reflux for 72 h then cooled to 18 °C and the DOWEX-50 was removed by filtration and washed with MeOH (3 × 10 mL). The combined filtrates were concentrated under reduced pressure and the aqueous residue diluted with brine (20 mL) and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic fractions were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash column chromatography (silica, 3:7 *v/v* EtOAc/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.2, 1:9 *v/v* EtOAc/hexane) afforded a *ca*. 1:1 mixture of the epimeric forms of the starting acetonide **329** (367 mg, 37% recovery). Thi material was identical, in all respects, with the authentic material.

Concentration of fraction B (R_f = 0.2, 1:1 *v/v* EtOAc/hexane) afforded a *ca*. 1:1 mixture of the epimeric forms of *diol* ***330*** (547 mg, 97% at 63% conversion) as a clear, colourless and viscous oil.

^{1}H NMR (300 MHz) δ 8.03 (d, *J* = 11.7 Hz, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 5.26 (s, 0.5H), 4.83 (m, 0.5H), 3.91 (broad t, *J* = 4.0 Hz, 1H), 3.49 (d, *J* = 8.2 Hz, 0.5H), 3.40 (d, *J* = 8.4 Hz, 0.5H), 2.81 (broad s, 2H), 2.09–1.19 (complex m, 13H), 1.03 (m, 1H).
^{13}C NMR (75 MHz) δ 166.1 (C), 165.9 (C), 132.7(9) (CH), 132.7(5) (CH), 130.8 (CH), 130.6 (CH), 129.4(5) (CH), 129.4(0) (CH), 128.3 (CH), 128.2 (CH), 74.8 (CH), 74.7 (CH), 73.5 (CH), 70.2 (CH), 68.4 (CH), 68.3 (CH), 35.5 (CH_2), 34.6 (C), 34.4 (C), 34.0 (CH_2), 33.3 (CH), 32.9 (CH_2), 31.8(2) (CH_2), 31.7(5) (CH), 31.7 (CH_2), 29.2 (CH_2), 28.8 (CH), 26.7 (CH_2), 25.0 (CH_2), 18.8 (two signals overlapping, 2 x CH_2), 17.4 (CH_2), 16.9 (CH_2) (signal due to one carbon obscured/overlapping).
IR ν_{max} 3407, 2934, 2865, 1713, 1450, 1315, 1277, 1175, 1115, 1070, 1026, 985, 713 cm^{-1}.
Mass spectrum (ES, +ve ion mode) *m/z* 339 [$(M + Na)^+$, 100%], 195 (11), 177 (41), 159 (49), 149 (18).
HRESMS Found: $(M + Na)^+$, 339.1583. $C_{19}H_{24}O_4$ requires $(M + Na)^+$, 339.1572.

(2*S*,4*R*,4a*S*,8a*S*)-4-Hydroxy-3-oxooctahydro-2*H*-2,4a-ethanonaphthalen-7-yl benzoate (331)



330 **331**

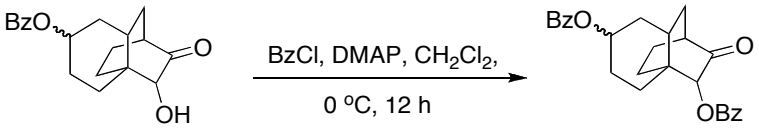
A solution of a *ca*. 1:1 mixture of the epimeric forms of diol **330** (1.20 g, 3.79 mmol) in CH_2Cl_2 (75 mL) was cooled to 0 °C while a solution of *p*-TsOH•H_2O (1.5 g, 7.96 mmol) and 4-acetamido-TEMPO (1.8 g, 8.44 mmol) in CH_2Cl_2 (75 mL) was prepared and allowed to stir at 18 °C for 30 min. The latter solution was then added to the first over 1.5 h and the ensuing mixture was stirred at 0 °C for a further 2.5 h, warmed to 18 °C then quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic fractions were washed with water (50 mL) and brine (50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 3:7 → 1:1 *v/v* EtOAc/hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.2, 1:1 *v/v* EtOAc/hexane) afforded a *ca*. 1:1 mixture of the epimeric forms of the starting diol **331** (253 mg, 21% recovery). This material was identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.4, 1:1 *v/v* EtOAc/hexane) afforded a *ca*. 1:1 mixture of the epimeric forms of the *title acyloin **331*** (888 mg, 94% at 79% conversion) as a clear, colourless and viscous oil.

^{1}H NMR (300 MHz) δ 8.03 (dm, *J* = 7.5 Hz, 2H), 7.54 (m, 1H), 7.43 (m, 2H), 5.33 (t, *J* = 2.7 Hz, 0.5H), 4.94 (m, 0.5H), 3.56 (d, *J* = 1.2 Hz, 0.5H), 3.47 (d, *J* = 1.7 Hz, 0.5H), 3.17 (broad s, 1H), 2.34 (broad t, *J* = 2.7 Hz, 1H), 2.18–1.51 (complex m, 11H), 1.39 (td, *J* = 13.7 and 3.9 Hz, 0.5H) and 1.23 (m, 1.5H).
^{13}C NMR (75 MHz) δ 218.5 (C), 218.3 (C), 165.9 (C), 165.6 (C), 132.8(2) (CH), 132.7(7) (CH), 130.6 (C), 130.4 (C), 129.4(2) (CH), 129.3(8) (CH), 128.3 (CH), 128.2 (CH), 80.7 (CH), 80.6 (CH), 73.0 (CH), 69.8 (CH), 41.2 (two signals overlapping, 2 x CH), 39.7 (CH), 39.4 (C), 35.4 (CH_2), 35.1 (CH_2), 34.1 (CH_2), 30.7 (CH), 30.2 (CH_2), 28.9 (two signals overlapping, 2 x CH_2), 26.8 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 25.0 (CH_2), 17.2 (CH_2), 16.8 (CH_2).
IR ν_{max} 3464, 2943, 2867, 1714, 1601, 1583, 1471, 1450, 1314, 1276, 1175, 1116, 1099, 1069, 1026, 984, 970, 912, 846, 834, 806, 714, 689 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 314 ($M^{+\bullet}$, 5%), 192 (93), 174 (20), 164 (30), 133 (38), 105 (100), 91 (29), 77 (52), 67 (15), 55 (14), 41 (16).
HREIMS Found: $M^{+\bullet}$, 314.1519. $C_{19}H_{22}O_4$ requires $M^{+\bullet}$, 314.1518.

(2*S*,4*R*,4a*S*,8a*S*)-3-Oxooctahydro-2*H*-2,4a-ethanonaphthalene-4,7-diyl dibenzoate (332)



331 **332**

A solution of a *ca*. 1:1 mixture of the epimeric forms of acyloin **331** (911 mg, 2.93 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (1.43 g, 11.7 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and treated with benzoyl chloride (1.0 mL, 8.61 mmol). The ensuing mixture was stirred for 2 h at 0 °C then $NaHCO_3$ (15 mL of a saturated aqueous solution) was added. The resulting biphasic system was warmed to 18 °C then stirred for 30 min at this temperature before being treated with CH_2Cl_2 (20 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic fractions were washed with brine (20 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure onto silica (*ca.* 2 g, 230–400 mesh). The resulting

free-flowing solid was subjected to flash column chromatography (1:4 *v/v* EtOAc/hexane elution) to afford a *ca*. 1:1 mixture of the epimeric forms of the *title* bis-*benzoate* ***332*** (990 mg, 82%) as a clear, colourless and viscous oil (R_f = 0.6, 1:1 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 8.05 (m, 4H), 7.57 (m, 2H), 7.45 (m, 4H), 5.35 (t, *J* = 2.2 Hz, 0.5H), 5.27 (s, 0.5H), 5.18 (s, 0.5H), 4.95 (m, 0.5H), 2.44 (t, *J* = 2.7 Hz, 1H), 2.29–1.25 (complex m, 13H).

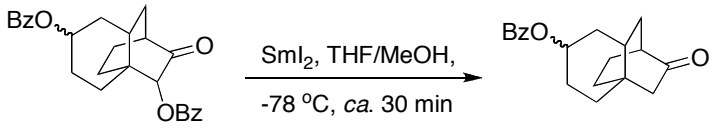
^{13}C NMR (75 MHz) δ 211.4 (C), 211.2 (C), 165.9 (C), 165.8 (C), 165.7 (C), 133.3 (CH), 133.0 (CH), 132.9 (CH), 130.4 (C), 129.9 (CH), 129.8 (CH), 129.5 (CH), 129.4 (C), 128.4(2) (CH), 128.3(8) (CH), 128.3 (CH), 79.8 (CH), 79.7 (CH), 72.7 (CH), 69.4 (CH), 41.9(2) (CH), 41.8(9) (CH), 39.2 (C), 38.9 (C), 35.3 (CH_2), 34.8 (CH), 34.0 (CH_2), 30.4(0) (CH), 30.3(8) (CH_2), 29.5(1) (CH_2), 29.4(8) (CH_2), 27.1 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 18.4 (CH_2), 17.9 (CH_2) (signals due to six carbons obscured/overlapping).

IR ν_{max} 2941, 2869, 1718, 1601, 1450, 1314, 1274, 1176, 1111, 1069, 1026, 989, 910, 803, 710 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 418 ($M^{+\bullet}$, 32%), 313 (15), 296 (25), 191 (29), 174 (15), 163 (19), 146 (23), 135 (30), 105 (100), 91 (21), 77 (70), 67 (14), 51 (19).

HREIMS Found: $M^{+\bullet}$, 418.1780. $C_{26}H_{26}O_5$ requires $M^{+\bullet}$, 418.1780.

(2*S*,4a*R*,8a*S*)-3-Oxooctahydro-2*H*-2,4a-ethanonaphthalen-7-yl benzoate (333)



332 **333**

A solution of a *ca*. 1:1 mixture of the epimeric forms of bis-benzoate **332** (900 mg, 2.15 mmol) in THF/MeOH (45 mL of a 2:1 *v/v* mixture) was cooled to –78 °C then SmI_2 (0.1 M solution in THF) was added dropwise until the blue colour persisted (depending on the quality of the samarium reagent up to 5 equivalents were required). Once addition was complete, the reaction mixture was allowed to stir at –78 °C for a further 15 min then poured into K_2CO_3 (20 mL of a saturated aqueous solution) and diluted with Et_2O (100 mL). The separated aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic fractions were washed with water (20 mL) and brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a *ca*. 1:1 mixture of the epimeric forms of *compound* ***333*** (641 mg, quant.) as a clear, colourless oil (R_f = 0.3, 3:7 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 8.00 (m, 2H), 7.51 (m, 1H), 7.39 (m, 2H), 5.28 (broad t, *J* = 2.2 Hz, 0.5H), 4.86 (tt, *J* = 11.2 and 4.6 Hz, 0.5H), 2.23–1.45 (complex m, 13H), 1.34 (m, 1H), 1.17 (m, 2H).

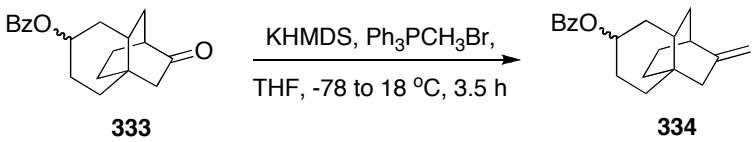
^{13}C NMR (75 MHz) δ 216.3 (C), 216.1 (C), 165.6 (C), 165.4 (C), 132.6(3) (CH), 132.5(8) (CH), 130.4 (C), 130.3 (C), 129.2(3) (CH), 129.1(8) (CH), 128.1 (CH), 128.0 (CH), 72.9 (CH), 69.6 (CH), 52.4 (CH_2), 51.7 (CH_2), 42.4 (CH), 42.2 (CH), 35.7 (CH), 35.4 (CH_2), 34.5 (CH_2), 34.3 (CH_2), 34.2 (C), 34.0 (C), 31.6 (CH), 31.5 (CH_2), 31.4 (CH_2), 31.0 (CH_2), 26.5 (CH_2), 24.9 (CH_2), 23.4 (CH_2), 23.0 (CH_2), 22.6 (CH_2) (signal due to one carbon obscured/overlapping).

IR ν_{max} 2940, 2867, 1714, 1601, 1583, 1473, 1450, 1401, 1339, 1314, 1275, 1238, 1174, 1113, 1097, 1069, 1025, 986, 967, 945, 714 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 298 ($M^{+\bullet}$, <1%), 176 (100), 148 (22), 133 (40), 122 (18), 105 (80), 91 (18), 77 (36).

HREIMS Found: $M^{+\bullet}$, 298.1567. $C_{19}H_{22}O_3$ requires $M^{+\bullet}$, 298.1569.

(2*S*,4a*R*,8a*S*)-3-Methyleneoctahydro-2*H*-2,4a-ethanonaphthalen-7-yl benzoate (334)



333 **334**

A suspension of methyltriphenylphosphonium bromide (862 mg, 2.41 mmol) in THF (10 mL) was treated dropwise with KHMDS (4.6 mL of a 0.5 M solution in THF, 2.28 mmol). The resulting bright-yellow reaction mixture was stirred at 18 °C for 1.5 h then cooled to –78 °C and a solution of a *ca*. 1:1 mixture of the epimeric forms of ketone **333** (400 mg, 1.34 mmol) in THF (3 mL) was added dropwise. The ensuing mixture was stirred at –78 °C for 1 h then warmed to 18 °C and stirred at this temperature for a further 2.5 h. After this time NH_4Cl (20 mL of a saturated aqueous solution) and Et_2O (100 mL) were added to the reaction mixture. The separated aqueous phase was extracted with Et_2O (2 × 50 mL) then the combined organic phases were washed with brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated, under reduced pressure, onto silica (*ca.* 500 mg, 230–400 mesh). The resulting free-flowing solid was subjected to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution) to afford a *ca*. 1:1 mixture of the epimeric forms of the *title alkene **334*** (335 mg, 84%) as a clear, colourless and viscous oil (R_f = 0.6, 3:7 *v/v* EtOAc/hexane).

^{1}H NMR (300 MHz) δ 8.05 (dm, *J* = 7.1 Hz, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.29 (broad qu, *J* = 2.7 Hz, 1H), 4.88 (m, 1H), 4.62 (broad q, *J* = 2.0 Hz, 1H), 2.15–1.00 (m, 16H).

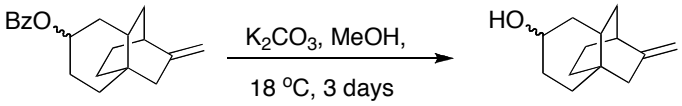
^{13}C NMR (75 MHz) δ 166.0 (C), 165.9 (C), 152.3 (C), 151.9 (C), 132.7 (two signals overlapping, 2 x CH), 131.0 (C), 130.8 (C), 129.5 (two signals overlapping, 2 x CH), 128.3 (CH), 128.2 (CH), 105.0 (CH_2), 104.9 (CH_2), 73.7 (CH), 70.5 (CH), 44.5 (CH_2), 43.9 (CH_2), 36.5 (CH), 36.2 (CH_2), 35.9 (CH), 35.8 (CH), 35.3 (CH_2), 35.2 (CH_2) 34.8 (CH_2), 32.3 (C), 32.2 (CH), 32.1 (C), 31.9 (CH_2), 27.3 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 25.6 (CH_2), 24.4 (CH_2), 23.9 (CH_2) (signal due to one carbon obscured/overlapping).

IR ν_{max} 2930, 2860, 1715, 1449, 1313, 1273, 1253, 1237, 1173, 1111, 1069, 1026, 987, 971, 868, 711, 693 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 296 ($M^{+\bullet}$, 12%), 277 (8), 256 (4), 174 (100), 159 (29), 145 (33), 131 (94), 105 (85), 91 (43), 77 (60), 41 (21).

HREIMS Found: $M^{+\bullet}$, 296.1777. $C_{20}H_{24}O_2$ requires $M^{+\bullet}$, 296.1776.

(2*S*,4a*R*,8a*S*)-3-Methyleneoctahydro-2*H*-2,4a-ethanonaphthalen-7-ol (335)



334 **335**

A solution of a *ca*. 1:1 mixture of the epimeric forms of benzoate **334** (355 mg, 1.20 mmol) in MeOH (10 mL) was treated with anhydrous K_2CO_3 (350 mg, 2.53 mmol). The ensuing mixture was stirred at 18 °C for 72 h then the MeOH was removed under a stream of nitrogen. The residue thus obtained was partitioned between brine (10 mL) and CH_2Cl_2 (20 mL) then the separated aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (silica, 1:1 *v/v* diethyl ether/pentane elution) and concentration of the appropriate fractions (R_f = 0.2, 1:1 *v/v* EtOAc/hexane) afforded a *ca*. 1:1 mixture of the epimeric forms of the *title alcohol **335*** (219 mg, 95%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 4.72 (qu, *J* = 2.2 Hz, 1H), 4.58 (qu, *J* = 2.0 Hz, 1H), 4.05 (m, 0.5H), 3.52 (m, 0.5H), 2.22–0.92 (complex m, 17H).

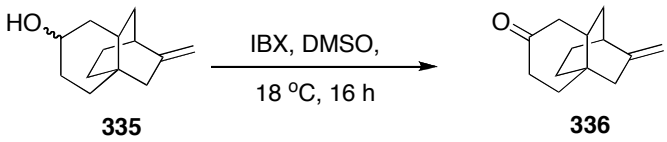
^{13}C NMR (75 MHz) δ 152.5 (C), 152.3 (C), 104.8 (CH_2), 104.7 (CH_2), 70.7 (CH), 66.5 (CH), 44.5 (CH_2), 43.9 (CH_2), 40.2 (CH_2), 37.8 (CH_2), 36.5 (CH), 36.0 (CH), 35.8 (CH), 35.5 (CH_2), 35.3 (two signals overlapping, 2 x CH_2), 32.5 (C), 32.0 (C), 31.1 (CH_2), 31.0 (CH), 30.8 (CH_2), 28.2 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 24.4 (CH_2), 23.8 (CH_2).

IR ν_{max} 3338, 2928, 2859, 1647, 1444, 1365, 1234, 1180, 1062, 1049, 1009, 919, 870 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 192 ($M^{+\bullet}$, 31%), 174 (71), 159 (30), 146 (41), 131 (100), 117 (20), 105 (35), 91 (51), 79 (31), 67 (16), 55 (15), 41 (29).

HREIMS Found: $M^{+\bullet}$, 192.1515. $C_{13}H_{20}O$ requires $M^{+\bullet}$, 192.1514.

(2*S*,4a*R*,8a*S*)-3-Methyleneoctahydro-7*H*-2,4a-ethanonaphthalen-7-one (336)



335 **336**

IBX (215 mg, 0.77 mmol) was added to DMSO (5 mL) and the resulting suspension stirred until complete dissolution had occurred (*ca.* 15 min). The solution so-formed was added to a *ca*. 1:1 mixture of the epimeric forms of alcohol **335** (98 mg, 0.51 mmol) and the ensuing mixture stirred for 16 h at 18 °C in the absence of light then diluted with water (10 mL) and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic fractions were washed with brine (10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 *v/v* diethyl ether/pentane elution) afforded, after concentration of the appropriate fractions (R_f = 0.5, 3:7 *v/v* EtOAc/hexane), the *title ketone* ***336*** (97 mg, quant.) as a white crystalline solid, m.p. = 57–59 °C.

^{1}H NMR (300 MHz) δ 4.77 (q, *J* = 2.2 Hz, 1H), 4.62 (q, *J* = 2.1 Hz, 1H), 2.51–2.09 (complex m, 7H), 2.02–1.63 (complex m, 6H), 1.53 (td, *J* = 13.7 and 4.9 Hz, 1H), 1.24 (m, 1H), 1.12 (ddd, *J* = 12.4, 5.2 and 2.1 Hz, 1H).

^{13}C NMR (75 MHz) δ 211.7 (C), 150.8 (C), 105.6 (CH_2), 46.3 (CH_2), 43.1 (CH_2), 38.8 (CH), 37.5 (CH_2), 36.8 (CH_2), 35.5(4) (CH_2), 35.4(8) (CH), 32.3 (C), 26.6 (CH_2), 24.0 (CH_2).

IR ν_{max} 2934, 2861, 1713, 1648, 1451, 1426, 1355, 1329, 1312, 1290, 1272, 1235, 1171, 1117, 876, 518 cm^{-1}.

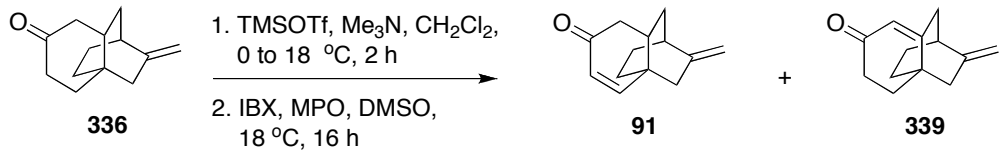
Mass spectrum (EI, 70 eV) *m/z* 190 ($M^{+\bullet}$, 100%), 175 (11), 161 (10), 147 (69), 133 (38), 119 (50), 105 (54), 91 (91), 79 (57), 77 (36), 55 (33), 41 (50).

HREIMS Found: $M^{+\bullet}$, 190.1356. $C_{13}H_{18}O$ requires $M^{+\bullet}$, 190.1358.

Elemental Analysis Found: C, 82.14; H, 9.49. $C_{13}H_{18}O$ requires C, 82.06; H, 9.49%.

Optical Rotation $[\alpha]_D$ = –28 (*c* 1.1, $CHCl_3$).

(2*S*,4a*R*,8a*S*)-3-Methylene-1,2,3,4,8,8a-hexahydro-7*H*-2,4a-ethanonaphthalen-7-one (91) and (2*S*,4a*R*)-3-methylene-1,2,3,4,5,6-hexahydro-7*H*-2,4a-ethanonaphthalen-7-one (339)



Following a protocol defined by Lalic and Corey,[190] a solution of ketone **336** (55 mg, 0.29 mmol) in CH_2Cl_2 (2.9 mL) was cooled to 0 °C then treated with Me_3N (325 μL, 3.50 mmol) and TMSOTf (300 μL, 1.74 mmol). The ensuing mixture was stirred at 0 °C for 1.5 h, warmed to 18 °C, stirred at this temperature for a further 30 min then diluted with pentane (50 mL). The resulting mixture was extracted with $NaHCO_3$ (10 mL of a saturated aqueous solution) and washed with brine (10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light-yellow oil. This crude mixture of silyl enol ethers was dissolved in DMSO (0.1 mL) then a solution of IBX and MPO (1.1 mL of a 0.4 M solution in DMSO, 0.44 mmol) was added. The resulting mixture was protected from light and allowed to stir at 18 °C for 16 h then poured into $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with EtOAc (5 × 10 mL). The combined organic fractions were washed with brine (10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 *v/v* EtOAc/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.5, 3:7 *v/v* EtOAc/hexane) afforded the *title enone* ***91*** (35 mg, 64%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.56 (d, *J* = 10.3 Hz, 1H), 5.87 (dd, *J* = 10.3 and 1.0 Hz, 1H), 4.83 (m, 1H), 4.68 (m, 1H), 2.49–1.95 (complex m, 7H), 1.83–1.66 (complex m, 3H), 1.50 (m, 1H), 1.19 (ddd, *J* = 12.5, 7.6 and 1.5 Hz, 1H).

^{13}C NMR (75 MHz) δ 200.2 (C), 156.7 (CH), 148.9 (C), 127.7 (CH), 106.9 (CH_2), 41.6 (CH_2), 40.8 (CH_2), 36.0 (CH), 35.5(4) (C), 35.4(6) (CH), 34.9 (CH_2), 26.4 (CH_2), 24.5 (CH_2).

IR ν_{max} 2938, 2865, 1682, 1469, 1449, 1429, 1414, 1391, 1272, 1251, 1235, 1167, 877, 766, 531 cm^{-1}.

Mass spectrum (EI, 70 eV) *m/z* 188 ($M^{+\bullet}$, 31%), 145 (19), 132 (29), 117 (16), 103 (23), 86 (89), 84 (85), 75 (16), 51 (100), 49 (92), 47 (95), 41 (37), 35 (73).

HRIEMS Found: $M^{+\bullet}$, 188.1201. $C_{13}H_{16}O$ requires $M^{+\bullet}$, 188.1201.

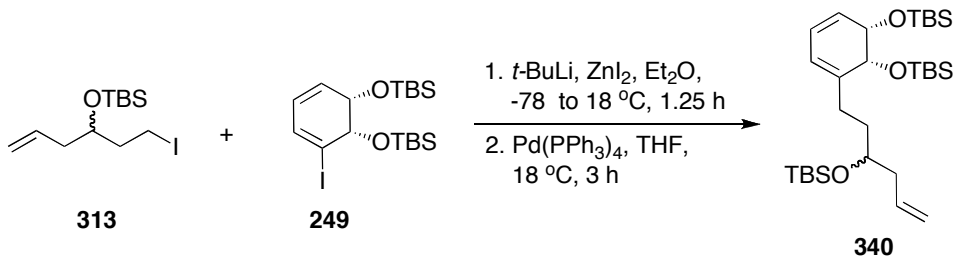
Optical Rotation $[\alpha]_D$ = +27 (*c* 0.9, $CHCl_3$) [lit.[178] $[\alpha]_D$ = +27.5 (*c* 0.83, $CHCl_3$)].

The data presented above matched the equivalent spectral information reported in the literature.[48,178]

Concentration of fraction B (R_f = 0.3, 3:7 *v/v* EtOAc/hexane) afforded the *title enone* ***339*** (12 mg, 21%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.84 (t, *J* = 1.8 Hz, 1H), 4.85 (m, 1H), 4.68 (m, 1H), 2.52–2.23 (complex m, 7H), 1.84–1.65 (complex m, 5H), 1.51 (m, 1H).
^{13}C NMR (75 MHz) δ 198.5 (C), 170.0 (C), 148.7 (CH_2), 124.1 (CH), 106.8 (CH_2), 39.8 (CH_2), 36.7 (CH), 36.4 (C), 36.3 (C), 33.9 (CH_2), 32.1 (CH_2), 30.3 (CH_2), 26.4 (CH_2).
IR ν_{max} 2935, 2859, 1670, 1627, 1448, 1420, 1362, 1329, 1313, 1262, 1248, 1211, 1194, 1181, 931, 913, 880, 847, 745, 611, 515 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 188 ($M^{+\bullet}$, 100%), 173 (11), 160 (29), 146 (60), 131 (51), 118 (70), 117 (65), 104 (44), 91 (60), 77 (35), 65 (34), 51 (20), 39 (39).
HRIEMS Found: $M^{+\bullet}$, 188.1203. $C_{13}H_{16}O$ requires $M^{+\bullet}$, 188.1201.
Optical Rotation $[\alpha]_D$ = +30 (*c* 0.7, $CHCl_3$).

({1-[2-((5*S*,6*R*)-5,6-bis{[*tert*-Butyl(dimethyl)silyl]oxy}cyclohexa-1,3-dien-1-yl)ethyl]but-3-en-1-yl}oxy)(*tert*-butyl)dimethylsilane (340)

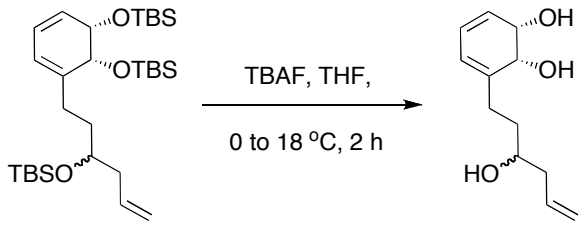


A solution of iodide **313** (211.3 mg, 0.621 mmol) in Et_2O (3 mL) was cooled to -78 °C and *t*-BuLi (804 μL of a 1.7 M solution in pentane, 1.37 mmol) was added dropwise over 4 min. After 3 min a solution of anhydrous ZnI_2 (683 μL of a freshly prepared 1.0 M solution in THF, 0.683 mmol) was added. The ensuing mixture was stirred at -78 °C for a further 10 min then allowed to warm to 18 ºC over 1 h. A solution of acetonide **249** (290 mg, 0.622 mmol) and $Pd(PPh_3)_4$ (72 mg, 0.062 mmol) in THF (3 mL) was then added dropwise to the reaction mixture to give a pale-yellow solution. After stirring for 3 h the now bright-yellow reaction mixture was quenched by addition of $NaHCO_3$ (10 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with Et_2O (3 x 20 mL). Combined organic phases were washed with brine (10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product as a yellow oil. Purification of this material by flash column

chromatography (silica, 1:99 *v/v* EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.6, 1:9 *v/v* EtOAc/hexane) afforded *ca*. 1:1 mixture of the epimeric forms of the *title compound* ***340*** (224 mg, 65%) as a colourless oil. This unstable material was used directly in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 5.89–5.76 (m, 2H), 5.73 (dd, *J* = 9.1 and 2.7 Hz, 1H), 5.63 (m, 1H), 5.04 (m, 2H), 4.16 (m, 1H), 3.94 (d, *J* = 4.8 Hz, 1H), 3.74 (m, 1H), 2.35–2.02 (m, 4H), 1.72–1.46 (m, 2H), 0.90 (s, 27H), 0.08 (s, 9H), 0.06 (s, 9H).
HREIMS Found: $M^{+\bullet}$, 552.3854. $C_{30}H_{60}O_3Si_3$ requires $M^{+\bullet}$, 552.3850.

(1*S*,2*R*)-3-(3-Hydroxyhex-5-en-1-yl)cyclohexa-3,5-diene-1,2-diol (341)



340 **341**

A solution of tris-silyl ether **340** (119.0 mg, 0.215 mmol) in THF (2 mL) was cooled to 0 ºC then treated with tetra-*n*-butyl ammonium fluoride (2 mL of a 1 M solution in THF, 2 mmol) The ensuing mixture was allowed to warm to 18 ºC and stirred at this temperature for 2 h then concentrated under reduced pressure. The brown residue thus obtained was subjected to flash column chromatography (silica, EtOAc then 1:9 *v/v* MeOH/DCM elution). Concentration of the appropriate fractions (R_f = 0.2, EtOAc) afforded a *ca*. 1:1 mixture of the epimeric forms of the *title triol* ***341*** (35.0 mg, 78%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.97–5.73 (m, 4H), 5.13 (d, *J* = 12.2 Hz, 2H), 4.27 (br s, 1H), 4.09 (t, *J* = 6.8 Hz, 1H), 3.70 (m, 1H), 2.80 (br s, 1H), 2.52–2.14 (m, 5H), 1.80–1.56 (m, 3H).
^{13}C NMR (75 MHz) δ 142.0 (C), 141.5 (C), 134.6 (two signals overlapping, 2 x CH), 127.6 (CH), 127.3 (CH), 125.1 (CH), 124.9 (CH), 119.8 (CH), 119.5 (CH), 118.3 (two signals overlapping, 2 x CH_2), 70.6 (CH), 70.5 (CH), 70.2 (two signals overlapping, 2 x CH), 69.0 (CH), 68.7 (CH), 42.2 (CH_2), 41.9 (CH_2), 35.4 (CH_2), 34.9 (CH_2), 30.2 (CH_2), 29.8 (CH_2).
IR ν_{max} 3360, 2923, 1429, 1401, 1259, 1148, 1066, 1023, 992, 917, 808 cm^{-1}.
Mass spectrum (EI, 70 eV) *m/z* 192 [$(M - H_2O)^{+\bullet}$, 47], 133 (67), 107 (100), 95 (35), 77 (52), 67 (25), 55 (25), 41 (46).
HREIMS Found: $M^{+\bullet}$, 210.1248. $C_{12}H_{18}O_3$ requires $M^{+\bullet}$, 210.1256.

References

(1) Gibson, D. T.; Subramanian, V., In *Microbial Degradation of Organic Compounds*; Gibson, D. T., Ed.; Marcel Dekker: New York, **1984**, p 181.

(2) Phale, P. S.; Basu, A.; Majhi, P. D.; Deveryshetty, J.; Vamsee-Krishna, C.; Shrivastava, R., *Omics- J. Integr. Biol.*, **2007**, *11*, 252.

(3) Gibson, D. T.; Koch, J. R.; Kallio, R. E., *Biochemistry*, **1968**, *7*, 2653.

(4) Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R. E., *Biochemistry*, **1968**, *7*, 3795.

(5) Johnson, R. A., *Org. React.*, **2004**, *63*.

(6) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J., *Biochemistry*, **1970**, *9*, 1626.

(7) Carless, H. A. J., *Tetrahedron: Asymmetry*, **1992**, *3*, 795.

(8) Sheldrake, G. N., In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley & Sons Ltd: New York, **1992**, p 127.

(9) Brown, S. M.; Hudlicky, T., In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI press Inc.: Greenwich, **1993**; Vol. 2, p 113.

(10) Hudlicky, T.; Gonzalez, D.; Gibson, D. T., *Aldrichimica Acta*, **1999**, *32*, 35.

(11) Boyd, D. R.; Sheldrake, G. N., *Nat. Prod. Rep.*, **1998**, *15*, 309.

(12) Zylstra, G. J.; Gibson, D. T., *J. Biol. Chem.*, **1989**, *264*, 14940.

(13) Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Brannigan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor, S. C., *J. Chem. Soc., Chem. Commun.*, **1995**, 117.

(14) Kobal, V. M.; Gibson, D. T.; Davis, R. E.; Garza, D. A., *J. Am. Chem. Soc.*, **1973**, *95*, 4420.

(15) Smith, M. B., In *Organic Synthesis*; Second ed.; McGraw Hill: New York, **2002**.

(16) Diels, O.; K., A., *Justus Liebigs Ann. Chem.*, **1928**, *460*, 98.

(17) Hoffmann, R.; Woodward, R. B., *J. Am. Chem. Soc.*, **1965**, *87*, 4388.

(18) Hoffmann, R.; Woodward, R. B., *J. Am. Chem. Soc.*, **1965**, *87*, 4389.

(19) Roush, W. R., In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, **1991**; Vol. 5, p 551.

(20) Jitkow, O. N.; Bogert, M. T., *J. Am. Chem. Soc.*, **1941**, *63*, 1979

(21) Gras, J. L.; Bertrand, M., *Tetrahedron Lett.*, **1979**, 4549.

(22) Fleming, I., *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons Ltd.: Chichester, **1978**.

(23) Ciganek, E., In *Organic Reactions*; Bauben, W. G., Boswell, G. A., Danishefsky, S., Gschwend, R. F., Hirschmann, R. F., Paquette, L. A., Posner, G. H., Reich, H. J., Eds.; John Wiley & Sons Ltd.: New York, **1984**; Vol. 32, p 1.

(24) Ogbomo, S. M.; Burnell, D. J., *Org. Biomol. Chem.*, **2006**, *4*, 3838.

(25) Mehta, G.; Uma, R., *Acc. Chem. Res.*, **2000**, *33*, 278.

(26) Stewart, S. G., *PhD Thesis*, The Australian National University, **2001**.

(27) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W., *Synlett*, **1991**, 741.

(28) Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1160.

(29) Hudlicky, T.; Boros, E. E.; Olivo, H. F.; Merola, J. S., *J. Org. Chem.*, **1992**, *57*, 1026.

(30) Hudlicky, T.; Seoane, G.; Pettus, T., *J. Org. Chem.*, **1989**, *54*, 4239.

(31) Hudlicky, T.; Boros, C. H.; Boros, E. E., *Synthesis*, **1992**, 174.

(32) Banwell, M. G.; Chun, C.; Edwards, A. J.; Vogtle, M. M., *Aust. J. Chem.*, **2003**, *56*, 861.

(33) Mihovilovic, M. D.; Leisch, H. G.; Mereiter, K., *Tetrahedron Lett.*, **2004**, *45*, 7087.

(34) Zezula, J.; Hudlicky, T.; Ghiviriga, I., *Collect. Czech. Chem. Commun.*, **2001**, *66*, 1269.

(35) Hudlicky, T.; Olivo, H. F., *Tetrahedron Lett.*, **1991**, *32*, 6077.

(36) Hudlicky, T.; Olivo, H. F., *J. Am. Chem. Soc.*, **1992**, *114*, 9694.

(37) Banwell, M. G.; Dupuche, J. R., *Chem. Commun.*, **1996**, 869.

(38) Banwell, M. G.; Darmos, P.; Mcleod, M. D.; Hockless, D. C. R., *Synlett*, **1998**, 897.

(39) Butora, G.; Gum, A. G.; Hudlicky, T.; Abboud, K. A., *Synthesis*, **1998**, 275.

(40) Banwell, M. G.; Hockless, D. C. R.; Holman, J. W.; Longmore, R. W.; McRae, K. J.; Pham, H. T. T., *Synlett*, **1999**, 1491.

(41) Banwell, M. G.; Edwards, A. J.; Mcleod, M. D.; Stewart, S. G., *Aust. J. Chem.*, **2004**, *57*, 641.

(42) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A., *Tetrahedron*, **2004**, *60*, 535.

(43) Banwell, M. G.; Harfoot, G. J., *Aust. J. Chem.*, **2004**, *57*, 895.

(44) Banwell, M. G.; Hockless, D. C. R.; Mcleod, M. D., *New J. Chem.*, **2003**, *27*, 50.

(45) Ogawa, S.; Takagaki, T., *J. Org. Chem.*, **1985**, *50*, 5075.

(46) Banwell, M. G.; Kokas, O. J.; Willis, A. C., *Org. Lett.*, **2007**, *9*, 3503.

(47) Matveenko, M.; Kokas, O. J.; Banwell, M. G.; Willis, A. C., *Org. Lett.*, **2007**, *9*, 3683.

(48) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J., *Angew. Chem., Int. Ed. Engl.*, **2008**, *47*, 1780.

(49) Hayashida, J.; Rawal, V. H., *Angew. Chem., Int. Ed. Engl.*, **2008**, *47*, 4373.

(50) Heatley, N. G.; Jennings, M. A.; Florey, H. W., *Br. J. Exp. Pathol.*, **1947**, *28*, 35.

(51) Comer, F. W.; Mccapra, F.; Quereshi, I. H.; Trotter, J.; Scott, A. I., *Chem. Commun.*, **1965**, 310.

(52) Comer, F. W.; Trotter, J., *J. Chem. Soc. B, Phys. Org.*, **1966**, 11.

(53) Comer, F. W.; Mccapra, F.; Qureshi, I. H.; Scott, A. I., *Tetrahedron*, **1967**, *23*, 4761.

(54) Mellows, G.; Mantle, P. G.; Feline, T. C.; Williams, D. J., *Phytochemistry*, **1973**, *12*, 2717.

(55) Kupka, J.; Anke, T.; Giannetti, B.-M.; Steglich, W., *Arch. Microbiol.*, **1981**, *130*, 223.

(56) Feline, T. C. M. G., *Chem. Commun.*, **1974**, 63.

(57) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S., *Tetrahedron Lett.*, **1976**, *17*, 195.

(58) Sakan, F.; Hashimoto, H.; Ichihara, A.; Shirahama, H.; Matsumoto, T., *Tetrahedron Lett.*, **1971**, *12*, 3703.

(59) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E., *Tetrahedron Lett.*, **1971**, *12*, 1829.

(60) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E., *Tetrahedron Lett.*, **1972**, *13*, 2053.

(61) Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T., *Tetrahedron Lett.*, **1974**, *15*, 3745.

(62) Trost, B. M.; Shuey, C. D.; Dininno, F.; Mcelvain, S. S., *J. Am. Chem. Soc.*, **1979**, *101*, 1284.

(63) Greene, A. E.; Luche, M. J.; Depres, J. P., *J. Am. Chem. Soc.*, **1983**, *105*, 2435.

(64) Schuda, P. F.; Phillips, J. L.; Morgan, T. M., *J. Org. Chem.*, **1986**, *51*, 2742.

(65) Yamazaki, M.; Shibasaki, M.; Ikegami, S., *Chem. Lett.*, **1981**, 1245.

(66) Yamazaki, M.; Shibasaki, M.; Ikegami, S., *J. Org. Chem.*, **1983**, *48*, 4402.

(67) Magnus, P.; Exon, C.; Albaugh-Robertson, P., *Tetrahedron*, **1985**, *41*, 5861.

(68) Singh, V.; Tosh, D. K.; Mobin, S. M., *Tetrahedron Lett.*, **2004**, *45*, 1729.

(69) Singh, V.; Pal, S.; Tosh, D. K.; Mobin, S. M., *Tetrahedron*, **2007**, *63*, 2446.

(70) Shibasaki, M.; Yamazaki, M.; Iseki, K.; Ikegami, S., *Tetrahedron Lett.*, **1982**, *23*, 5311.

(71) Greene, A. E.; Luche, M. J.; Serra, A. A., *J. Org. Chem.*, **1985**, *50*, 3957.

(72) Nishida, M.; Iseki, K.; Shibasaki, M.; Ikegami, S., *Chem. Pharm. Bull.*, **1990**, *38*, 3230.

(73) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2439.

(74) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N., *Synlett*, **1990**, 169.

(75) Toda, M.; Yamamura, S.; Hirata, Y.; Hayashi, M., *Bull. Chem. Soc. Jpn.*, **1972**, *45*, 264.

(76) Barton, D. H. R.; Mccombie, S. W., *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.

(77) Luche, J. L., *J. Am. Chem. Soc.*, **1978**, *100*, 2226.

(78) Reekie, T. A.; Austin, K. A. B.; Banwell, M. G.; Willis, A. C., *Aust. J. Chem.*, **2008**, *61*, 94.

(79) Ohgi, T.; Kondo, T.; Goto, T., *Tetrahedron Lett.*, **1977**, *18*, 4051.

(80) Angyal, S. J.; Beveridge, R. J., *Carbohydr. Res.*, **1978**, *65*, 229.

(81) Konosu, T.; Oida, S., *Chem. Pharm. Bull.*, **1991**, *39*, 2212.

(82) Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R., *Tetrahedron Lett.*, **1986**, *27*, 3827.

(83) Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J., *J. Org. Chem.*, **1986**, *51*, 789.

(84) Ho, P. T., *Tetrahedron Lett.*, **1978**, 1623.

(85) Seto, H.; Mander, L. N., *Synth. Commun.*, **1992**, *22*, 2823.

(86) Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M., *J. Org. Chem.*, **1994**, *59*, 6338.

(87) Harfoot, G. J., *PhD Thesis*, The Australian National University, **2004**.

(88) Molander, G. A.; Hahn, G., *J. Org. Chem.*, **1986**, *51*, 1135.

(89) Hwang, J.-T.; Liao, C.-C., *Tetrahedron Lett.*, **1991**, *32*, 6583.

(90) Demuth, M.; Schaffner, K., *Angew. Chem., Int. Ed. Engl.*, **1982**, *21*, 820.

(91) Zimmerman, H. E.; Armesto, D., *Chem. Rev.*, **1996**, *96*, 3065.

(92) Houk, K. N., *Chem. Rev.*, **1976**, *76*, 1.

(93) Demuth, M. M., Gamal, *Synthesis*, **1989**, 145.

(94) Singh, V. K.; Deota, P. T.; Bedekar, A. V., *J. Chem. Soc., Perkin Trans. 1*, **1992**, 903.

(95) Demuth, M., In *Photochemical Key Steps in Organic Synthesis - an Experimental Coursebook*; Mattay, J., Griesbeck, A., Eds.; VCH Publishers Inc.: New York, **1994**, p 74.

(96) Sammes, P. G., *Tetrahedron*, **1976**, *32*, 405.

(97) Batey, R. A.; Motherwell, W. B., *Tetrahedron Lett.*, **1991**, *32*, 6211.

(98) Nowitzki, O.; Munnich, I.; Stucke, H.; Hoffmann, H. M. R., *Tetrahedron*, **1996**, *52*, 11799.

(99) Ito, Y.; Hirao, T.; Saegusa, T., *J. Org. Chem.*, **1978**, *43*, 1011.

(100) Crimmins, M. T.; Mascarella, S. W., *J. Am. Chem. Soc.*, **1986**, *108*, 3435.

(101) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I., *J. Am. Chem. Soc.*, **1976**, *98*, 2346.

(102) Frigerio, M.; Santagostino, M.; Sputore, S., *J. Org. Chem.*, **1999**, *64*, 4537.

(103) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S., *J. Am. Chem. Soc.*, **2000**, *122*, 7596.

(104) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A., *Angew. Chem., Int. Ed. Engl.*, **1971**, *10*, 330.

(105) Danishefsky, S.; Kitahara, T.; Mckee, R.; Schuda, P. F., *J. Am. Chem. Soc.*, **1976**, *98*, 6715.

(106) Abraham, W. R., *Curr. Med. Chem.*, **2001**, *8*, 583.

(107) Stadler, M.; Anke, T.; Dasenbrock, J.; Steglich, W., *Z Naturforsch C*, **1993**, *48*, 545.

(108) Opatz, T.; Kolshorn, H.; Birnbacher, J.; Schuffler, A.; Deininger, F.; Anke, T., *Eur. J. Org. Chem.*, **2007**, 5546.

(109) Lorenzen, K.; Anke, T., *Curr. Org. Chem.*, **1998**, *2*, 329.

(110) Banwell, M. G.; Mcrae, K. J.; Willis, A. C., *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2194.

(111) Banwell, M.; Mcleod, M., *Chem. Commun.*, **1998**, 1851.

(112) Austin, K. A. B.; Banwell, M. G.; Harfoot, G. J.; Willis, A. C., *Tetrahedron Lett.*, **2006**, *47*, 7381.

(113) Taber, D. F., *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: Heidelberg, **1984**.

(114) Bear, B. R.; Sparks, S. M.; Shea, K. J., *Angew. Chem., Int. Ed. Engl.*, **2001**, *40*, 821.

(115) Boyd, D. R.; Hand, M. V.; Sharma, N. D.; Chima, J.; Dalton, H.; Sheldrake, G. N., *J. Chem. Soc., Chem. Commun.*, **1991**, 1630.

(116) Boyd, D. R.; Sharma, N. D.; Byrne, B.; Hand, M. V.; Malone, J. F.; Sheldrake, G. N.; Blacker, J.; Dalton, H., *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1935.

(117) Hudlicky, T.; Boros, E. E., *Tetrahedron: Asymmetry*, **1992**, *3*, 217.

(118) Heguaburu, V.; S·, M. M.; Schapiro, V.; Pandolfi, E., *Tetrahedron Lett.*, *In Press, Corrected Proof*.

(119) Forman, G., *PhD Thesis*, The Australian National University, **1998**.

(120) Farina, V.; Krishnamurthy, V., In *Organic Reactions*; Paquette, L. A., Beak, P., Ciganek, E., Curran, D., Czarnik, A. W., Denmark, S. E., Hegedus, L., Kelly, R. C., Overman, L. E., Roush, W., Smith III, A. B., White, J. D., Eds.; John Wiley and Sins Inc.: New York, **1997**; Vol. 50.

(121) Krohn, K.; Freund, C.; Florke, U., *Eur. J. Org. Chem.*, **1998**, 2713.

(122) Kim, S.; Fuchs, P. L., *J. Am. Chem. Soc.*, **1993**, *115*, 5934.

(123) Oppolzer, W.; Snowden, R. L.; Simmons, D. P., *Helv. Chim. Acta*, **1981**, *64*, 2002.

(124) Pimm, A.; Kocienski, P.; Street, S. D. A., *Synlett*, **1992**, 886.

(125) Negishi, E.; Hu, Q.; Huang, Z. H.; Qian, M. X.; Wang, G. W., *Aldrichimica Acta*, **2005**, *38*, 71.

(126) Kaugars, G., In *Encyclopedia of Reagents for Organic Syntehsis*; Paquette, L. A., Ed.; John Wiley & Sons Ltd.: West Sussex, **1995**, p 1191.

(127) Greshock, T. J.; Funk, R. L., *Tetrahedron Lett.*, **2006**, *47*, 5437.

(128) He, Y.; Funk, R. L., *Org. Lett.*, **2006**, *8*, 3689.

(129) Taylor, E. C.; Lamattina, J. L., *J. Org. Chem.*, **1978**, *43*, 1200.

(130) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H., *J. Org. Chem.*, **1999**, *64*, 8267.

(131) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y. B.; Albizati, K. F., *J. Am. Chem. Soc.*, **1990**, *112*, 6965.

(132) Huckin, S. N.; Weiler, L., *Can. J. Chem., Rev. Can. Chim*, **1974**, *52*, 2157.

(133) Krantz, A.; Lin, C. Y., *J. Am. Chem. Soc.*, **1973**, *95*, 5662.

(134) Ouellett, R. J.; Booth, G. E., *J. Org. Chem.*, **1965**, *30*, 423.

(135) Spitzner, D., *Angew. Chem., Int. Ed. Engl.*, **1978**, *17*, 197.

(136) Hagiwara, H.; Okano, A.; Uda, H., *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2109.

(137) Reusch, W. H., In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Ltd.: West Sussex, **1995**, p 2311.

(138) Mironov, G. S.; Orlova, I. M.; Farberov, M. I., *J. Gen. Chem., USSR*, **1963**, *33*, 1476.

(139) Johnson, P. Y.; Berchtold, G. A., *J. Org. Chem.*, **1970**, *35*, 584.

(140) Reed, S. F., *J. Org. Chem.*, **1962**, *27*, 4116.

(141) Rickerby, J.; Vallet, M.; Bernardinelli, G.; Viton, F.; Kundig, E. P., *Chem. Eur. J.*, **2007**, *13*, 3354.

(142) Rottlander, M.; Boymond, L.; Cahiez, G.; Knochel, P., *J. Org. Chem.*, **1999**, *64*, 1080.

(143) Vu, V. A.; Berillon, L.; Knochel, P., *Tetrahedron Lett.*, **2001**, *42*, 6847.

(144) Ren, H. J.; Krasovskiy, A.; Knochel, P., *Chem. Commun.*, **2005**, 543.

(145) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I., *Tetrahedron Lett.*, **1986**, *27*, 4025.

(146) Briere, J.-F.; Blaauw, R. H.; Benningshof, J. C. J.; Ginkel, A. E. V.; Maarseveen, J. H. V.; Hiemstra, H., *Eur. J. Org. Chem.*, **2001**, *2001*, 2371.

(147) McRae, K. J., *PhD Thesis*, The Australian National University, **2001**.

(148) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Morita, Y.; Noyori, R., *Isr. J. Chem.*, **1984**, *24*, 118.

(149) Suzuki, M.; Yanagisawa, A.; Noyori, R., *J. Am. Chem. Soc.*, **1988**, *110*, 4718.

(150) Karplus, M., *J. Am. Chem. Soc.*, **1963**, *85*, 2870.

(151) Ganguly, R. N.; Trivedi, G. K.; Bhattacharyya, S. C., *Indian J Chem B*, **1978**, *16*, 23.

(152) Weyerstahl, P.; Marschall, H.; Splittgerber, U.; Wolf, D., *Flavour Frag J*, **2000**, *15*, 61.

(153) Jefferies, P. R.; Middleton, E. J.; Knox, J. R., *Aust. J. Chem.*, **1962**, *15*, 532.

(154) Oh, Y. L.; Maslen, E. N., *Tetrahedron Lett.*, **1966**, 3291.

(155) Fukushi, Y.; Yajima, C.; Mizutani, J.; Tahara, S., *Phytochemistry*, **1998**, *49*, 593.

(156) Barrero, A. F.; Del Moral, J. Q.; Lara, A., *Tetrahedron*, **2000**, *56*, 3717.

(157) Fukuyama, Y.; Shida, N.; Kodama, M., *Tetrahedron Lett.*, **1995**, *36*, 583.

(158) Huang, J. M.; Yokoyama, R.; Yang, C. S.; Fukuyama, Y., *J. Nat. Prod.*, **2001**, *64*, 428.

(159) Lu, R. H.; Paul, C.; Basar, S.; Konig, W. A., *Tetrahedron: Asymmetry*, **2005**, *16*, 883.

(160) Groweiss, A.; Fenical, W.; He, C. H.; Clardy, J.; Wu, Z. D.; Yiao, Z. N.; Long, K. H., *Tetrahedron Lett.*, **1985**, *26*, 2379.

(161) Qi, S. H.; Zhang, S.; Yang, L. H.; Qian, P. Y., *Nat Prod Res*, **2008**, *22*, 154.

(162) Norte, M.; Fernandez, J. J.; Souto, M. L., *Tetrahedron Lett.*, **1994**, *35*, 4607.

(163) Paul, C.; Konig, W. A.; Muhle, H., *Phytochemistry*, **2001**, *57*, 307.

(164) Wang, J.; Kodali, S.; Lee, S. H.; Galgoci, A.; Painter, R.; Dorso, K.; Racine, F.; Motyl, M.; Hernandez, L.; Tinney, E.; Colletti, S. L.; Herath, K.; Cummings, R.; Salazar, O.; Gonzalez, I.; Basilio, A.; Vicente, F.; Genilloud, O.; Pelaez, F.; Jayasuriya, H.; Young, K.; Cully, D. F.; Singh, S. B., *Proc. Natl. Acad. Sci. U. S. A.*, **2007**, *104*, 7612.

(165) Young, K.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K.; Zhang, C. W.; Kodali, S.; Galgoci, A.; Painter, R.; Brown-Driver, V.; Yamamoto, R.; Silver, L. L.; Zheng, Y. C.; Ventura, J. I.; Sigmund, J.; Ha, S.; Basilio, A.; Vicente, F.; Tormo, J. R.; Pelaez, F.; Youngman, P.; Cully, D.; Barrett, J. F.; Schmatz, D.; Singh, S. B.; Wang, J., *Antimicrob. Agents Chemother.*, **2006**, *50*, 519.

(166) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C. W.; Hernandez, L.; Allocco, J.; Basilio, A.; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B., *Nature*, **2006**, *441*, 358.

(167) Giannis, A., *Chem. Eng. News*, **2006**, *84*, 8.

(168) Manallack, D. T.; Crosby, I. T.; Khakham, Y.; Capuano, B., *Curr. Med. Chem.*, **2008**, *15*, 705.

(169) Yao, Y. S.; Yao, Z. J., *Chinese J Org Chem*, **2008**, *28*, 1553.

(170) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Montero, A.; Edmonds, D. J., *Angew. Chem., Int. Ed. Engl.*, **2007**, *46*, 4712.

(171) Krauss, J.; Knorr, V.; Manhardt, V.; Scheffels, S.; Bracher, F., *Arch Pharm*, **2008**, *341*, 386.

(172) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C. W.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J., *J. Am. Chem. Soc.*, **2006**, *128*, 15547.

(173) Jayasuriya, H.; Herath, K. B.; Zhang, C.; Zink, D. L.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Gonzalez, I.; Salazar, O.; Pelaez, F.; Cummings, R.; Ha, S.; Wang, J.; Singh, S. B., *Angew. Chem., Int. Ed. Engl.*, **2007**, *46*, 4684.

(174) Herath, K.; Attygalle, A. B.; Singh, S. B., *Tetrahedron Lett.*, **2008**, *49*, 5755.

(175) Herath, K. B.; Attygalle, A. B.; Singh, S. B., *J. Am. Chem. Soc.*, **2007**, *129*, 15422.

(176) Campbell, J. W.; Cronan, J. E., *Annu Rev Microbiol*, **2001**, *55*, 305.

(177) Yun, S. Y.; Zheng, J. C.; Lee, D., *Angew. Chem., Int. Ed. Engl.*, **2008**, *47*, 6201.

(178) Tiefenbacher, K.; Mulzer, J., *Angew. Chem., Int. Ed. Engl.*, **2008**, *47*, 6199.

(179) Waalboer, D. C. J.; Schaapman, M. C.; Van Delft, F. L.; Rutjes, F. P. J. T., *Angew. Chem., Int. Ed. Engl.*, **2008**, *47*, 6576.

(180) Nicolaou, K. C.; Toh, Q. Y.; Chen, D. Y. K., *J. Am. Chem. Soc.*, **2008**, *130*, 11292.

(181) Austin, K. A. B.; Banwell, M. G.; Willis, A. C., *Org. Lett.*, **2008**, *10*, 4465.

(182) Nicolaou, K. C.; Li, A.; Edmonds, D. J., *Angew. Chem., Int. Ed. Engl.*, **2006**, *45*, 7086.

(183) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S., *Angew. Chem., Int. Ed. Engl.*, **2007**, *46*, 3942.

(184) Huang, Y.; Iwama, T.; Rawal, V. H., *J. Am. Chem. Soc.*, **2000**, *122*, 7843.

(185) Ferraboschi, P.; Canevotti, R.; Grisenti, P.; Santaniello, E., *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2301.

(186) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K., *Synthesis*, **1980**, 807.

(187) Slomp, G.; Johnson, J. L., *J. Am. Chem. Soc.*, **1958**, *80*, 915.

(188) Trost, B. M.; Machacek, M. R.; Tsui, H. C., *J. Am. Chem. Soc.*, **2005**, *127*, 7014.

(189) Moser, W. H., *Tetrahedron*, **2001**, *57*, 2065.

(190) Lalic, G.; Corey, E. J., *Org. Lett.*, **2007**, *9*, 4921.

(191) Gillard, J. R.; Burnell, D. J., *J. Chem. Soc., Chem. Commun.*, **1989**, 1439.

(192) Pollard, D. J.; Woodley, J. M., *Trends Biotechnol*, **2007**, *25*, 66.

(193) Banwell, M. G.; Dupuche, J. R.; Gable, R. W., *Aust. J. Chem.*, **1996**, *49*, 639.

(194) Boyd, D. R.; Sharma, N. D.; Llamas, N. M.; Malone, J. F.; O'Dowd, C. R.; Allen, C. C. R., *Org. Biomol. Chem.*, **2005**, *3*, 1953.

(195) Hon, Y.-S.; Wong, Y.-C.; Chang, C.-P.; Hsieh, C.-H., *Tetrahedron*, **2007**, *63*, 11325.

(196) Bertus, P.; Drouin, L.; Laroche, C.; Szymoniak, J., *Tetrahedron*, **2004**, *60*, 1375.

(197) Boyd, D. R.; Sharma, N. D.; Llamas, N. M.; O'Dowd, C. R.; Allen, C. C. R., *Org. Biomol. Chem.*, **2006**, *4*, 2208.

(198) Parks, B. W.; Gilbertson, R. D.; Domaille, D. W.; Hutchison, J. E., *J. Org. Chem.*, **2006**, *71*, 9622.

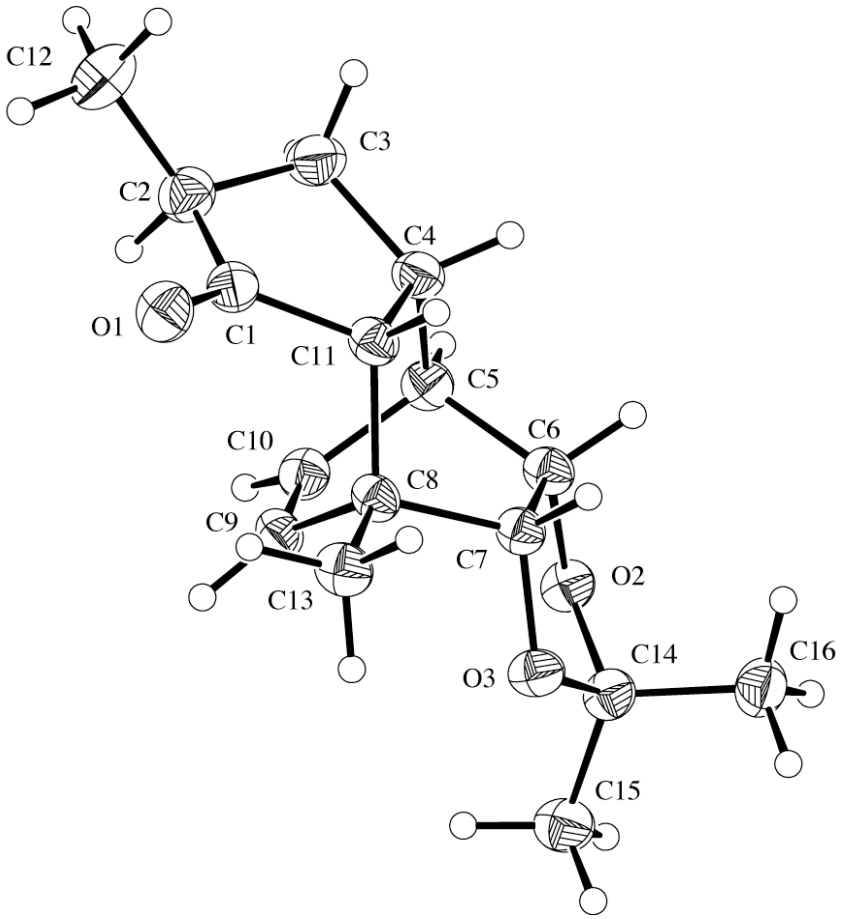
(199) Smith, A. B.; Beauchamp, T. J.; Lamarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K., *J. Am. Chem. Soc.*, **2000**, *122*, 8654.

A.1 Appendix one

X-ray crystal structure report for compound 139

A full X-ray crystallographic report for compound **139** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 139.pdf

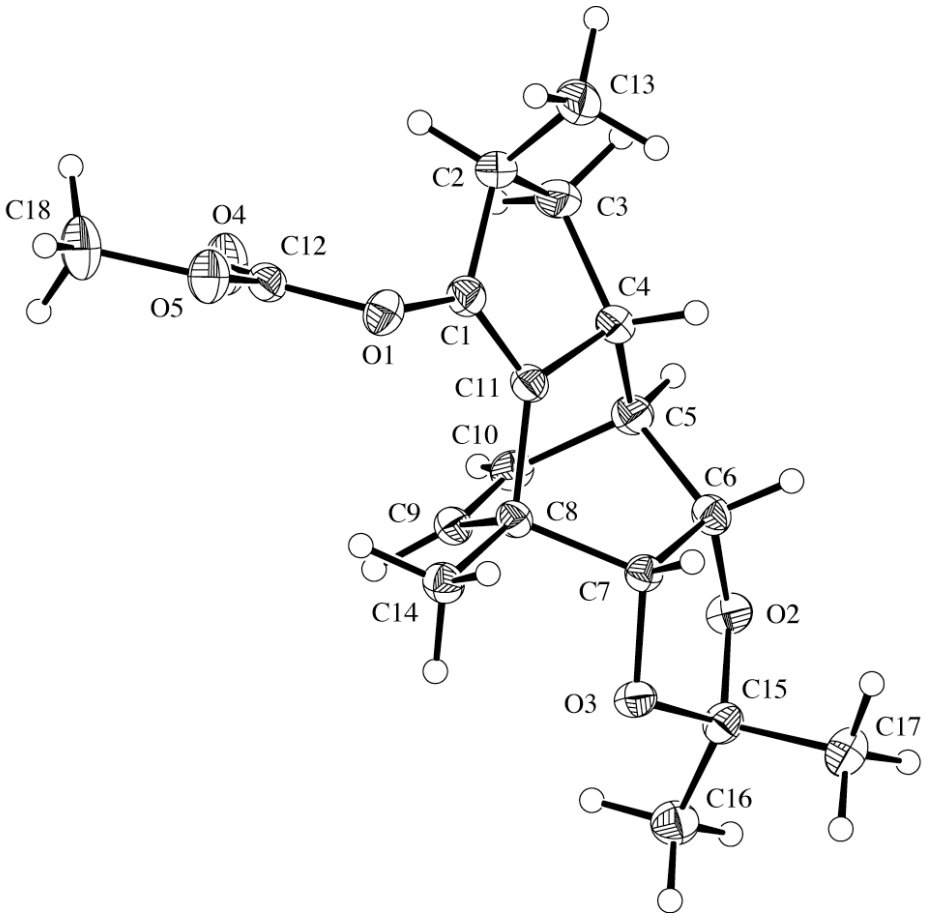


A.2 Appendix two

X-ray crystal structure report for compound 141

A full X-ray crystallographic report for compound **141** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 141.pdf

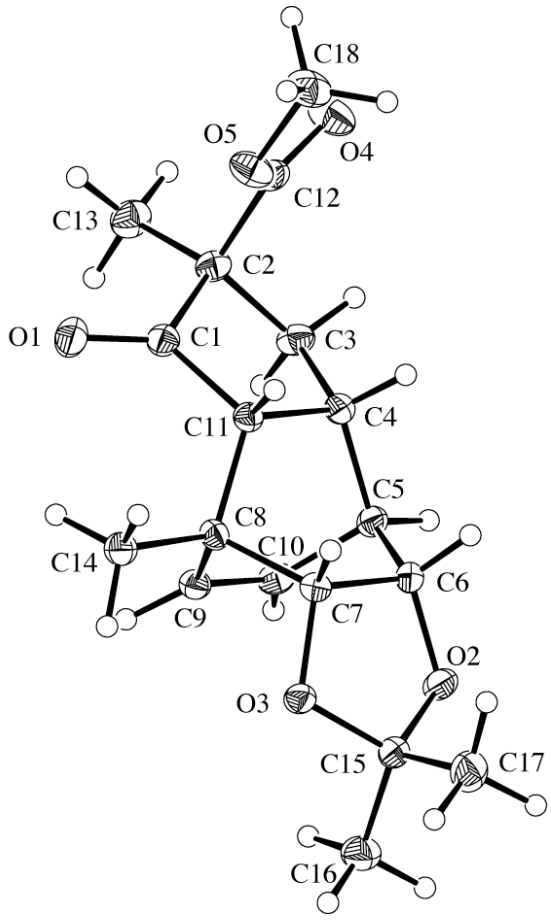


A.3 Appendix three

X-ray crystal structure report for compound 133

A full X-ray crystallographic report for compound **133** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 133.pdf

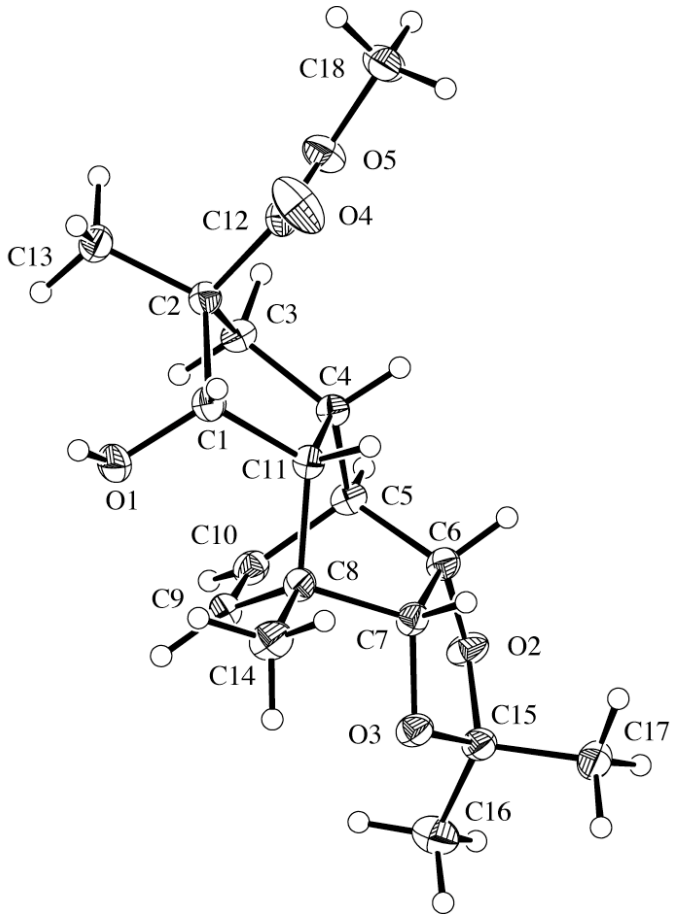


A.4 Appendix four

X-ray crystal structure report for compound 144

A full X-ray crystallographic report for compound **144** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 144.pdf

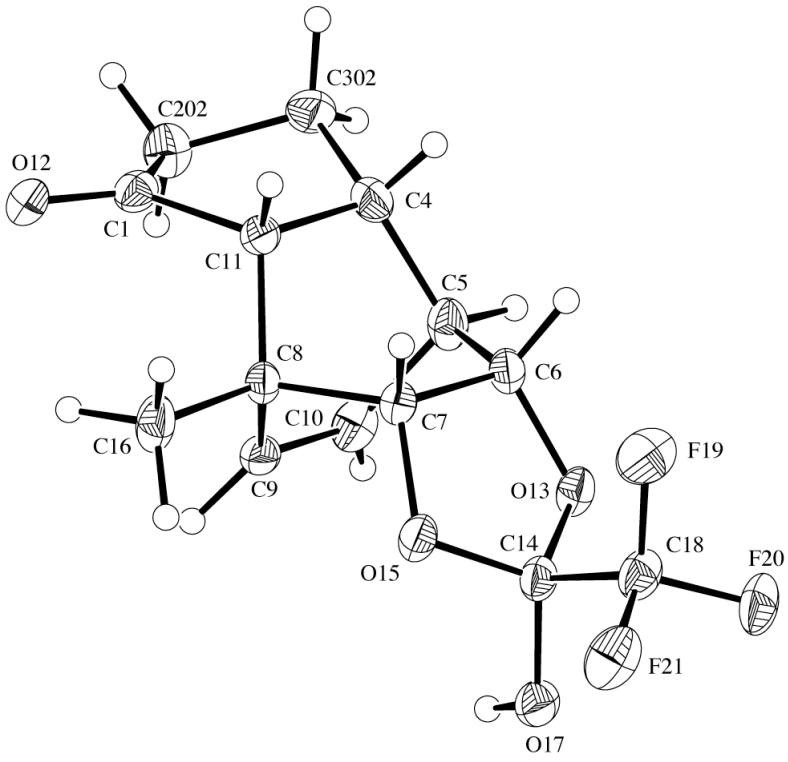


A.5 Appendix five

X-ray crystal structure report for compound 147

A full X-ray crystallographic report for compound **147** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 147.pdf

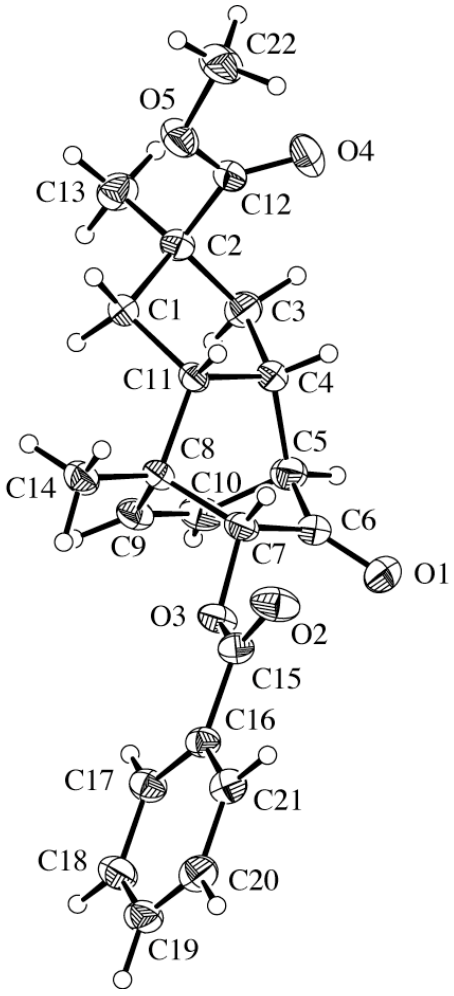


A.6 Appendix six

X-ray crystal structure report for compound 150

A full X-ray crystallographic report for compound **150** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 150.pdf

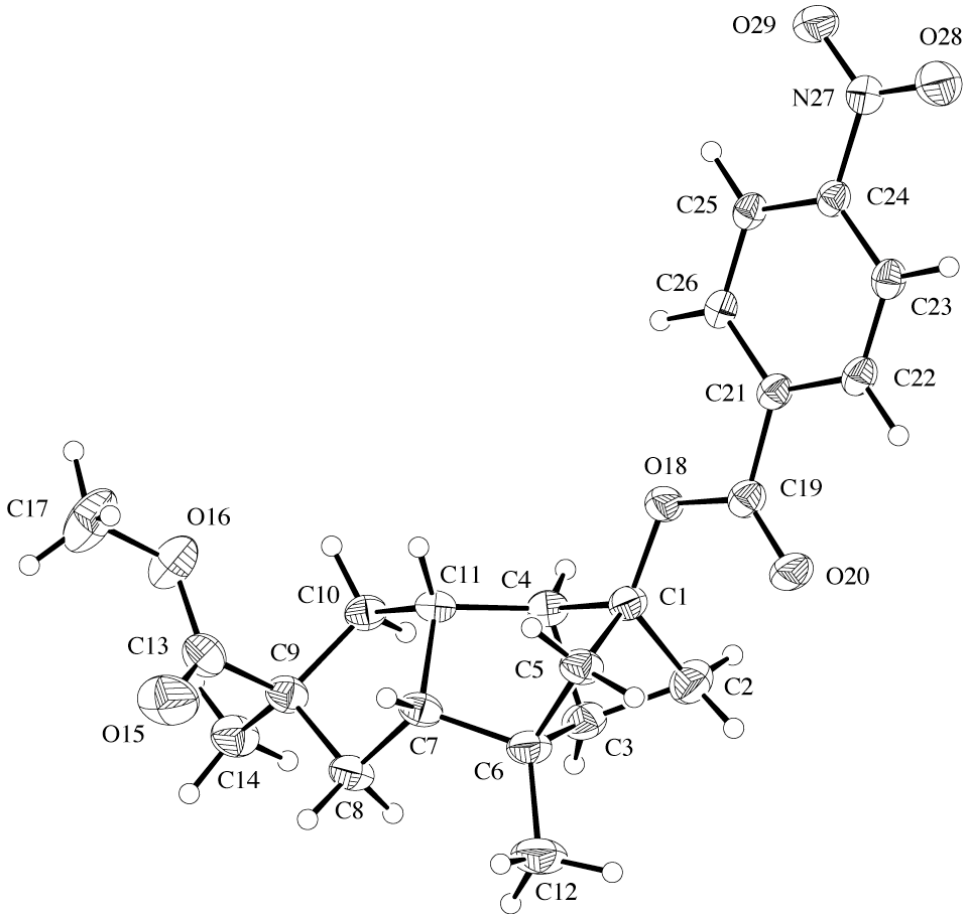


A.7 Appendix seven

X-ray crystal structure report for compound 157a

A full X-ray crystallographic report for compound **157a** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 157a.pdf

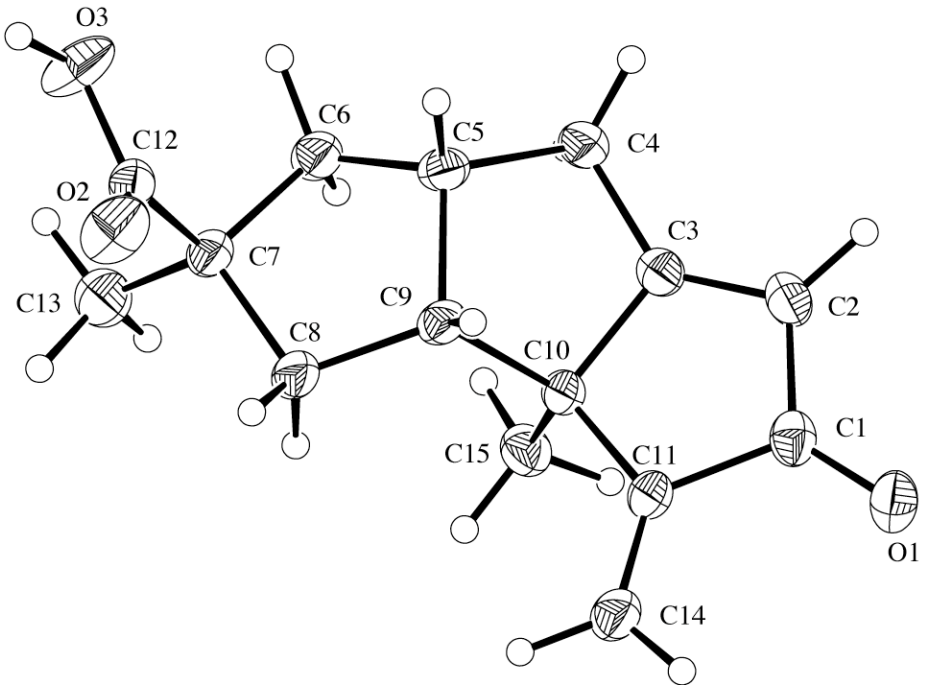


A.8 Appendix eight

X-ray crystal structure report for compound 136

A full X-ray crystallographic report for compound **136** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 136.pdf

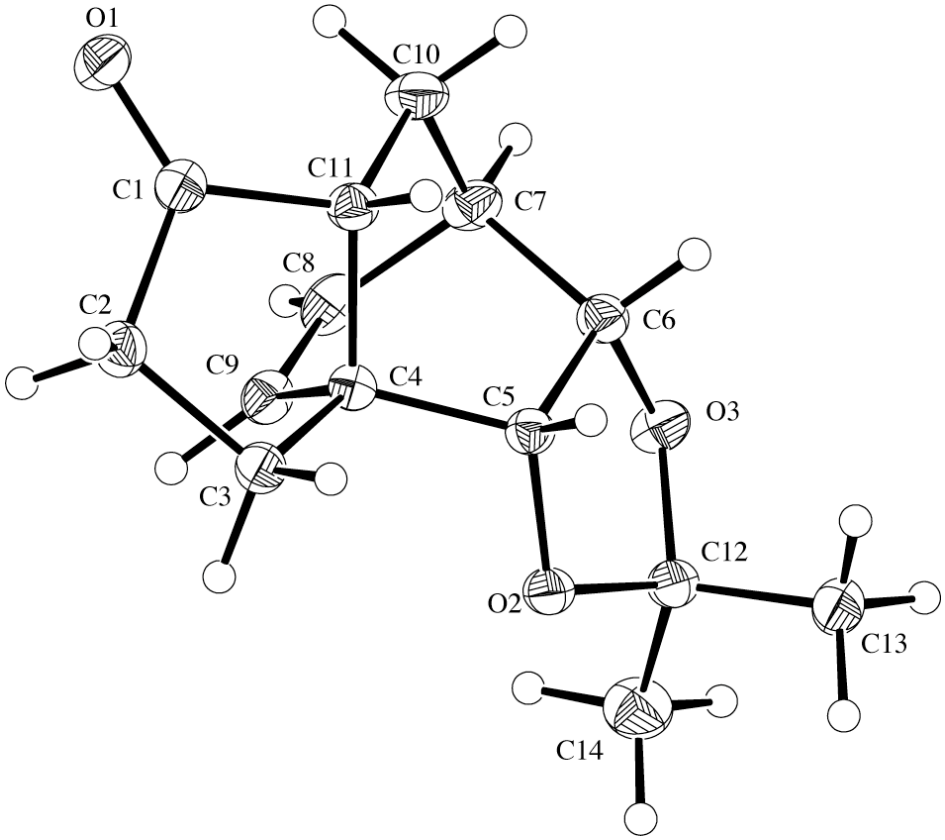


A.9 Appendix nine

X-ray crystal structure report for compound 229

A full X-ray crystallographic report for compound **229** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 229.pdf

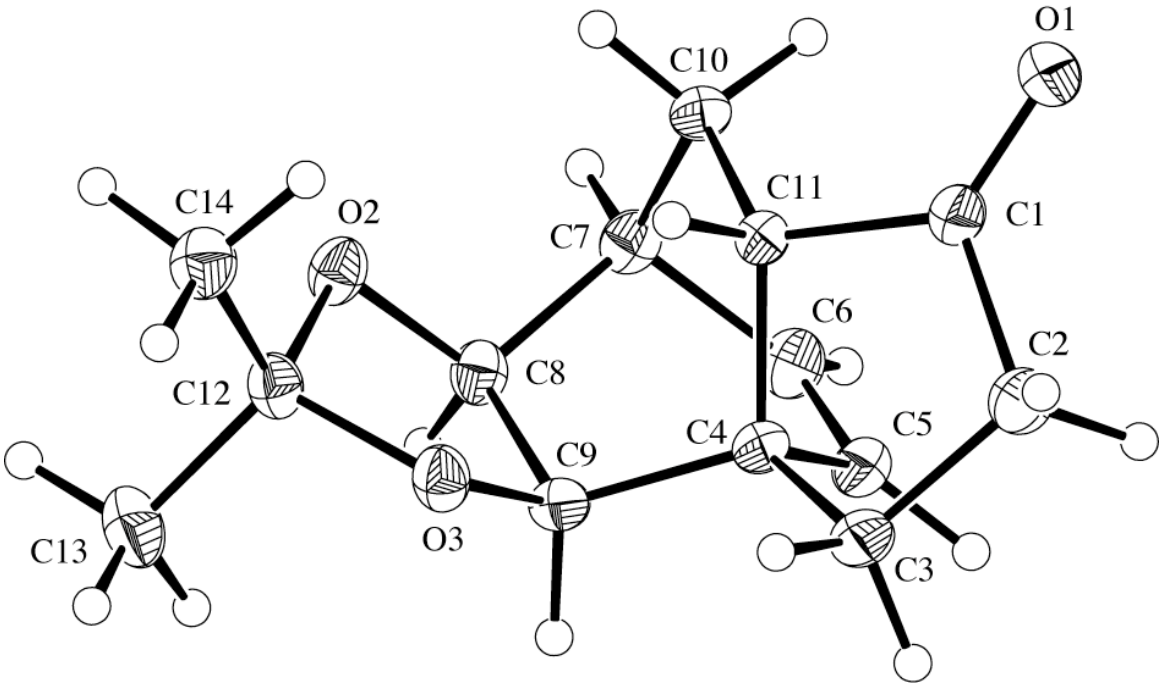


A.10 Appendix ten

X-ray crystal structure report for compound 230

A full X-ray crystallographic report for compound **230** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 230.pdf

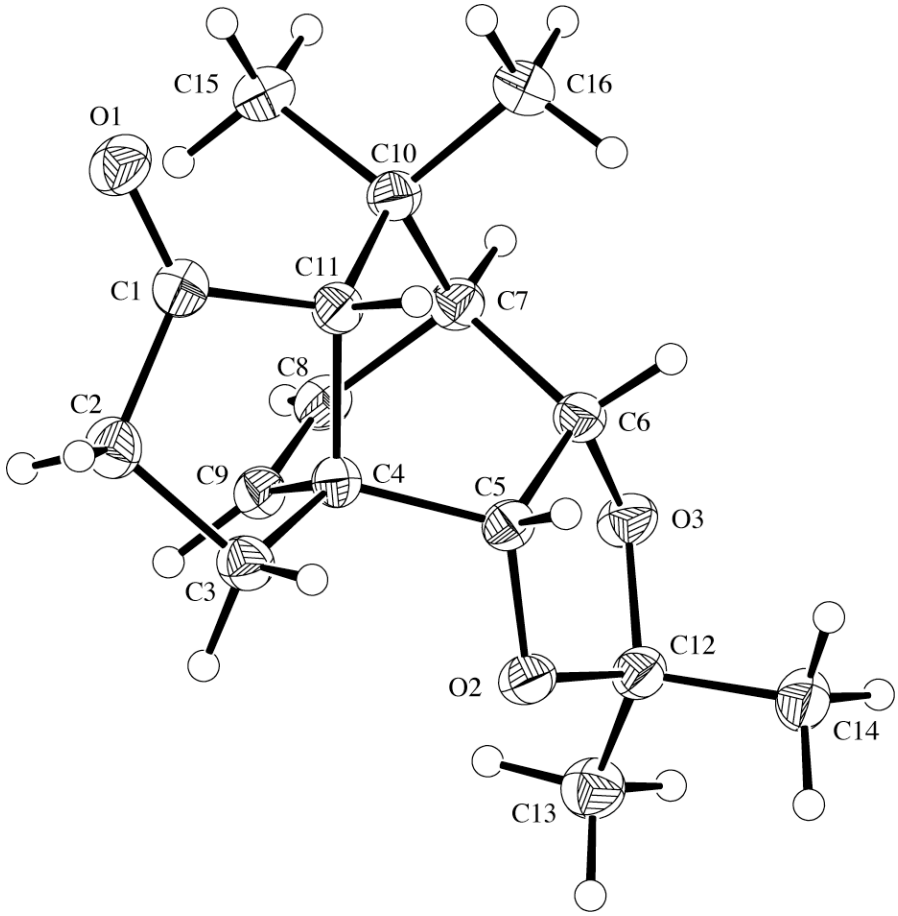


A.11 Appendix eleven

X-ray crystal structure report for compound 237

A full X-ray crystallographic report for compound **237** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 237.pdf

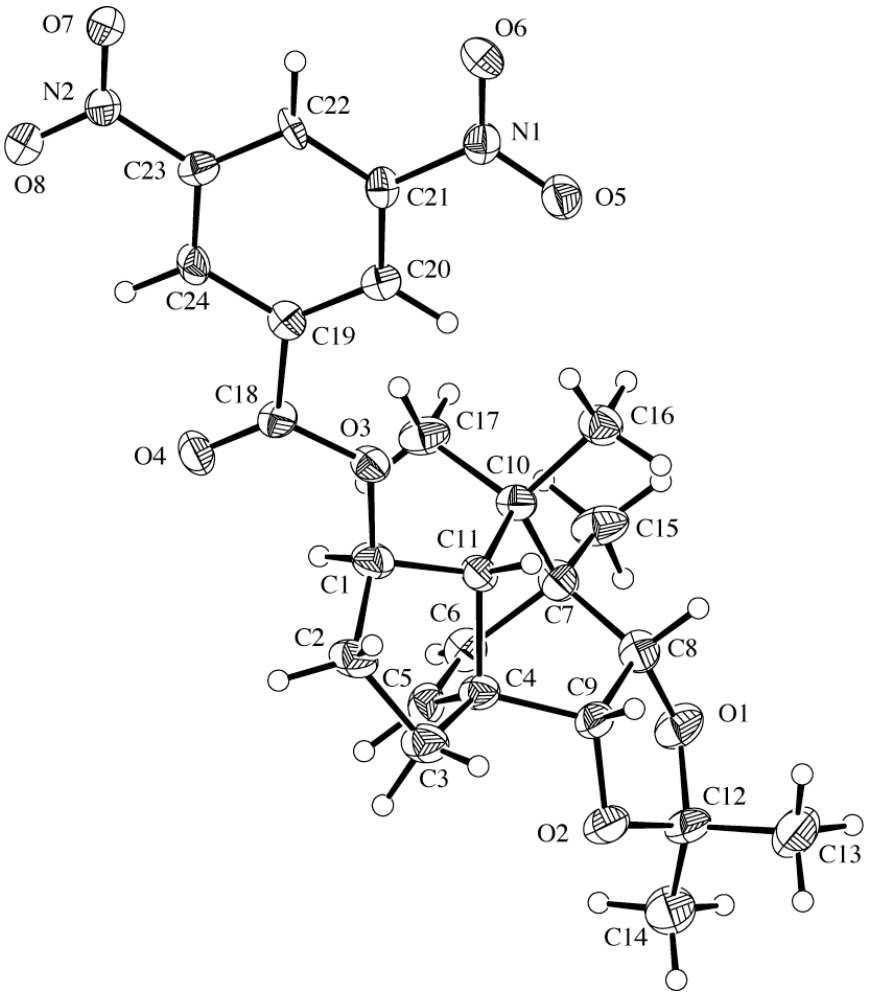


A.12 Appendix twelve

X-ray crystal structure report for compound 256a

A full X-ray crystallographic report for compound **256a** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 256a.pdf

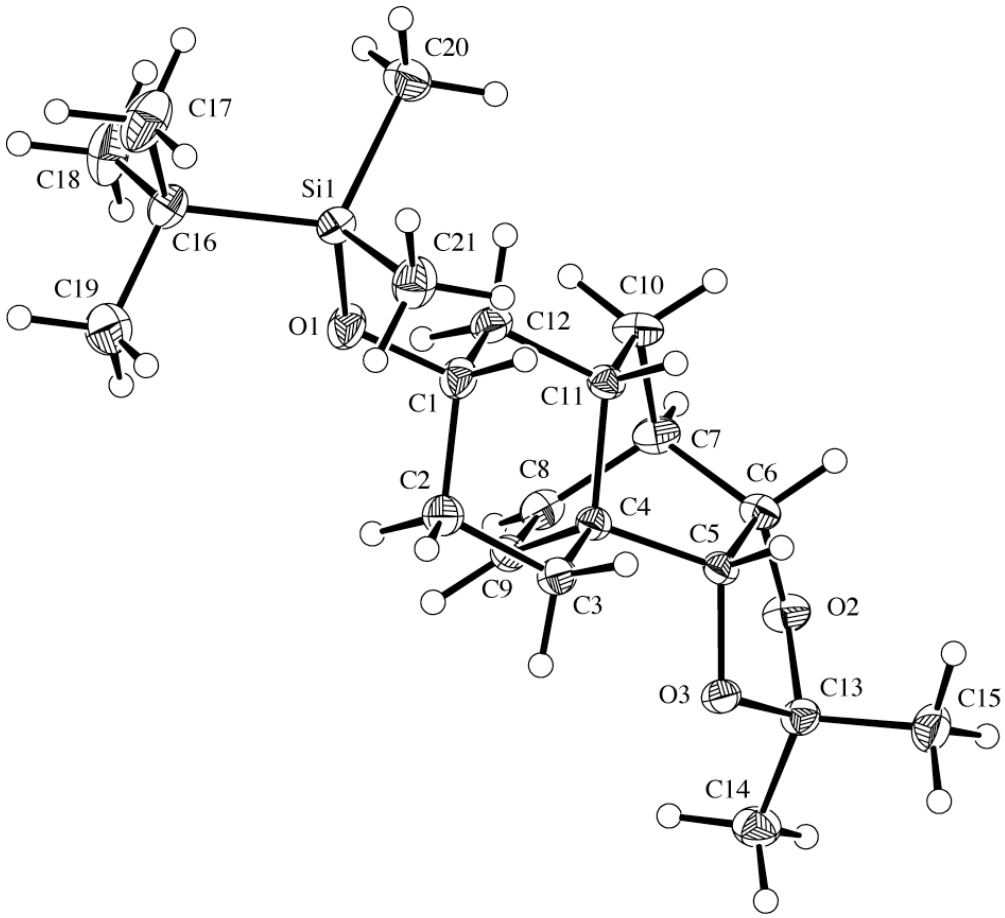


A.13 Appendix thirteen

X-ray crystal structure report for compound 319

A full X-ray crystallographic report for compound **319** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 319.pdf

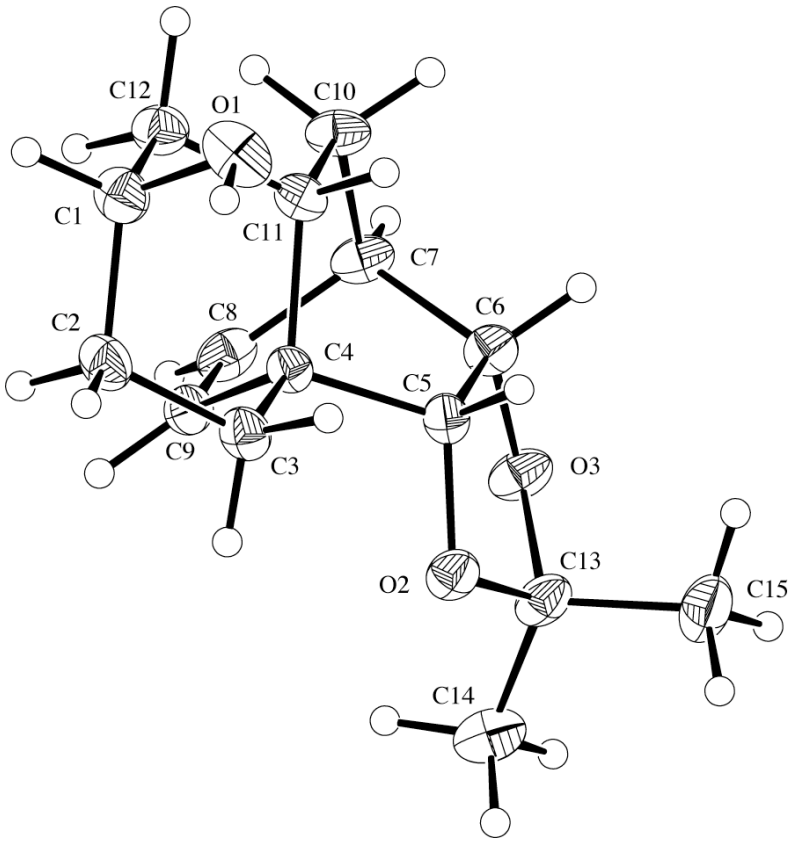


A.14 Appendix fourteen

X-ray crystal structure report for compound 323

A full X-ray crystallographic report for compound **323** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 323.pdf

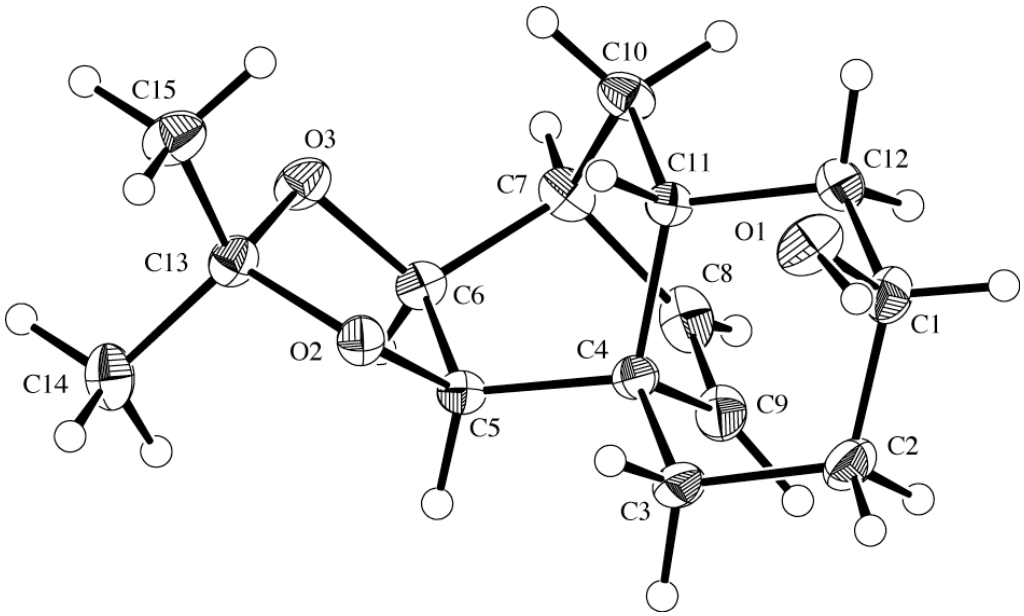


A.15 Appendix fifteen

X-ray crystal structure report for compound 324

A full X-ray crystallographic report for compound **324** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 324.pdf

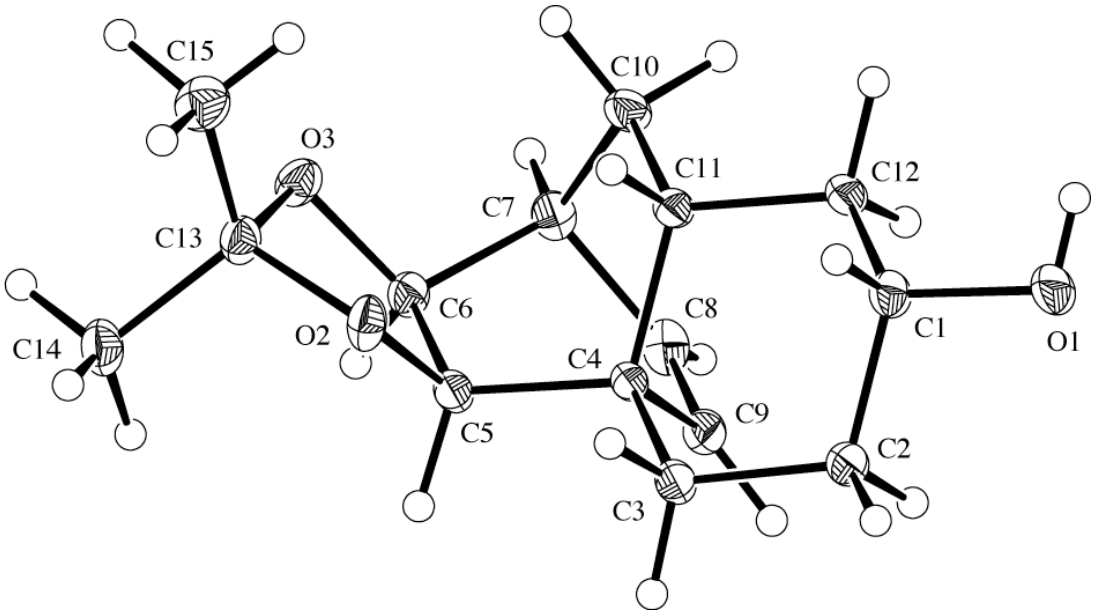


A.16 Appendix sixteen

X-ray crystal structure report for compound 325

A full X-ray crystallographic report for compound **325** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 325.pdf



A.17 Appendix seventeen

X-ray crystal structure report for compound 336

A full X-ray crystallographic report for compound **336** (as complied by Anthony C. Willis of the Australian National University) is provided in PDF-format on the compact disc found on the inside back cover of this thesis.

X-ray report 336.pdf